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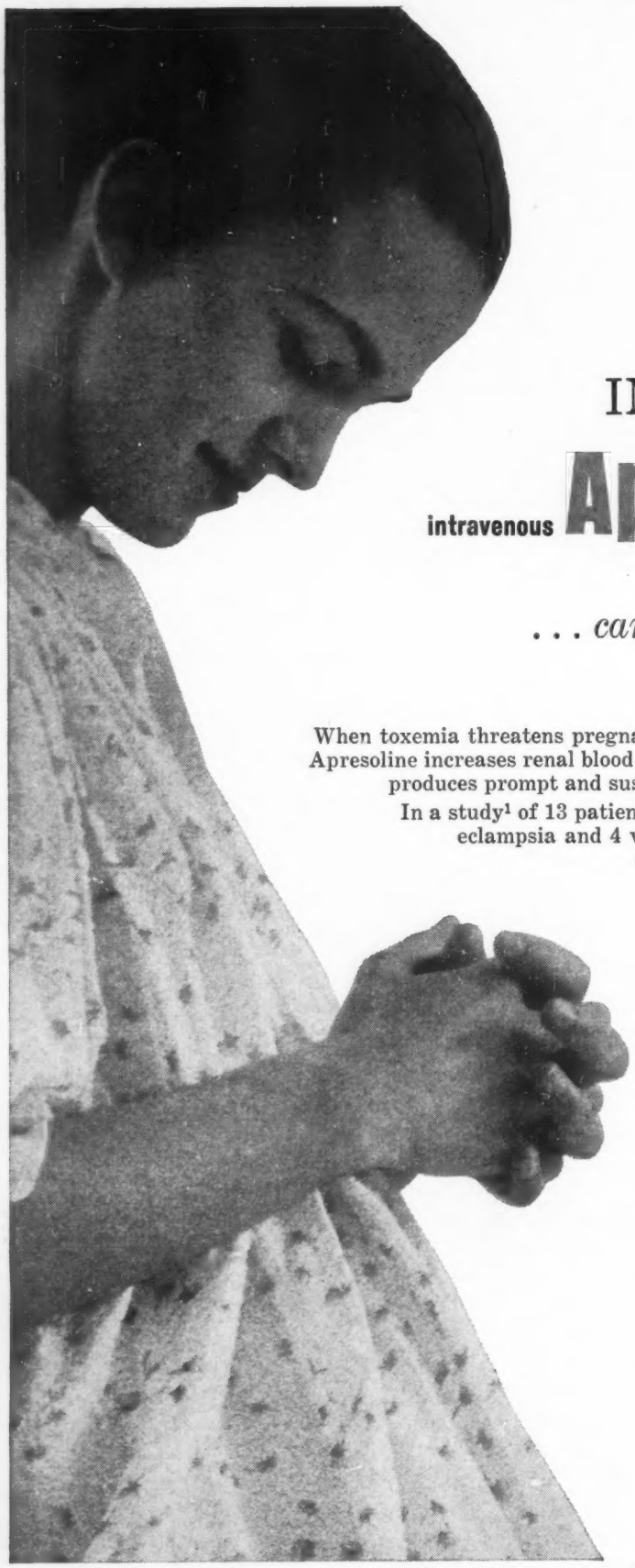
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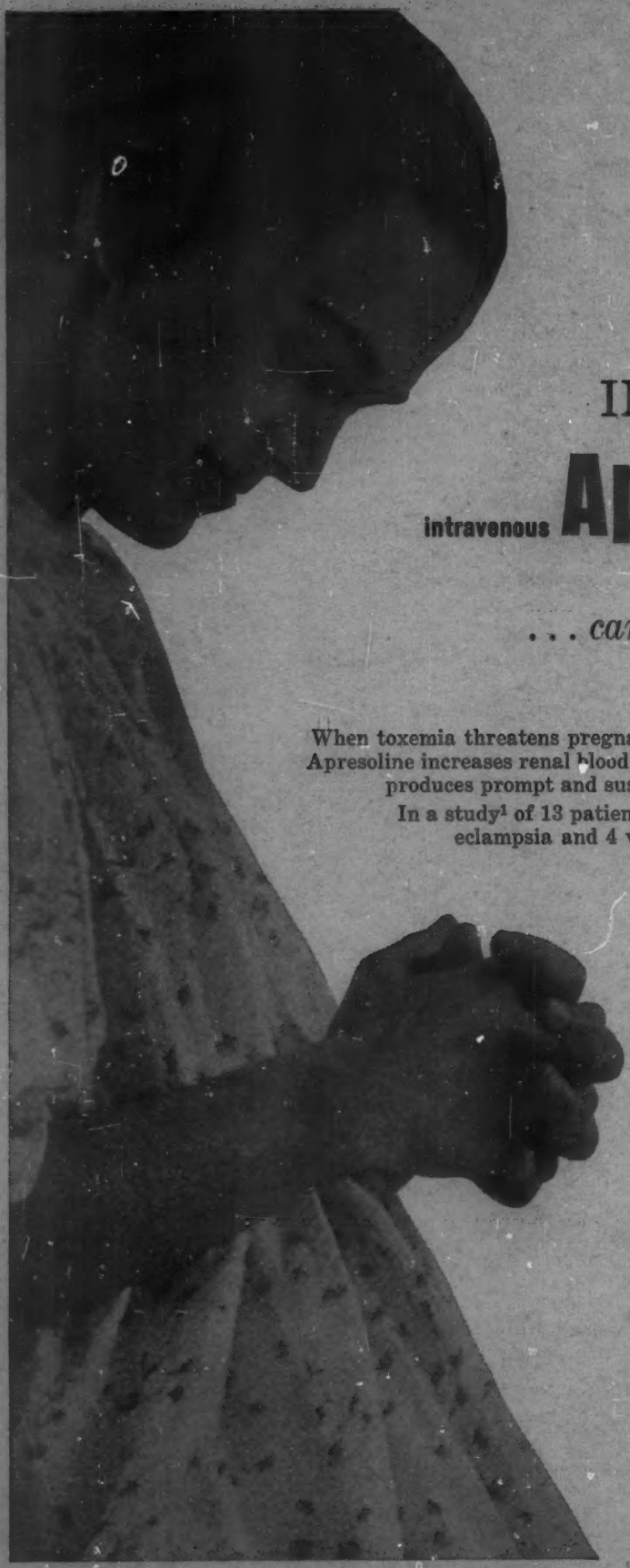
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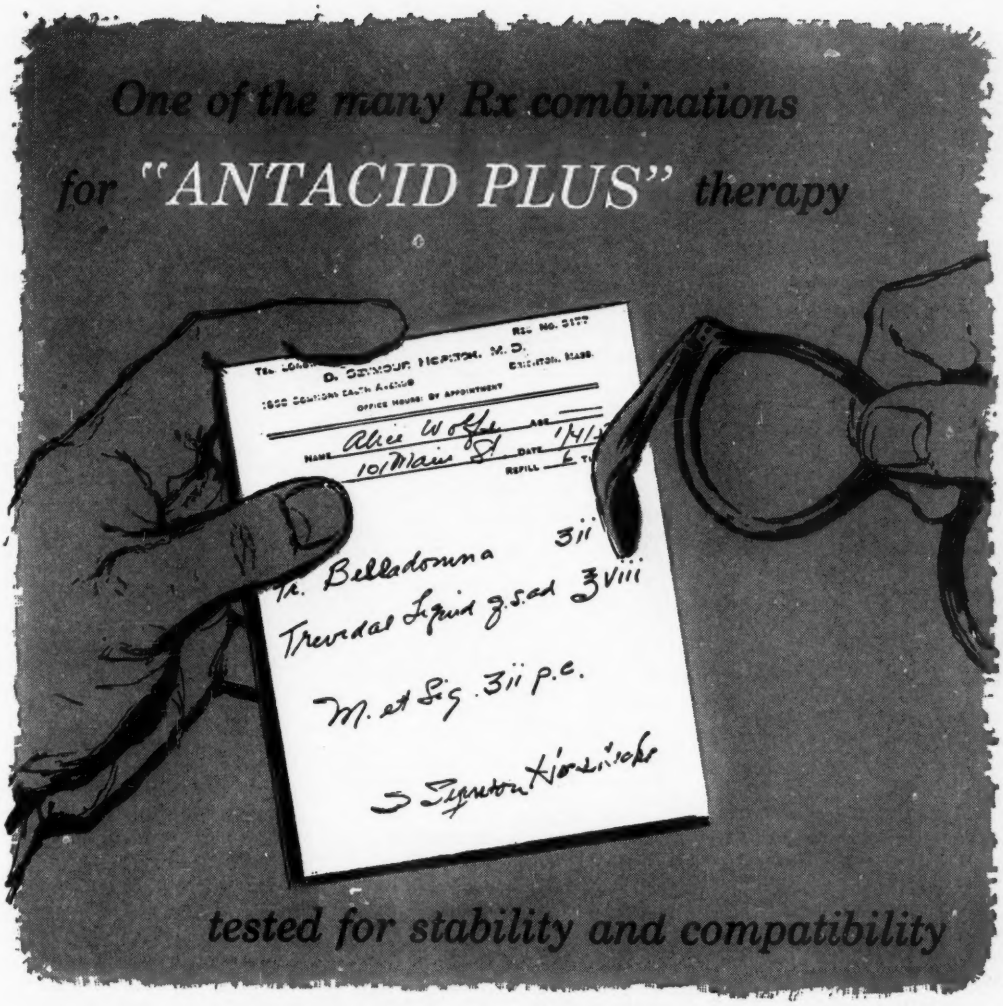
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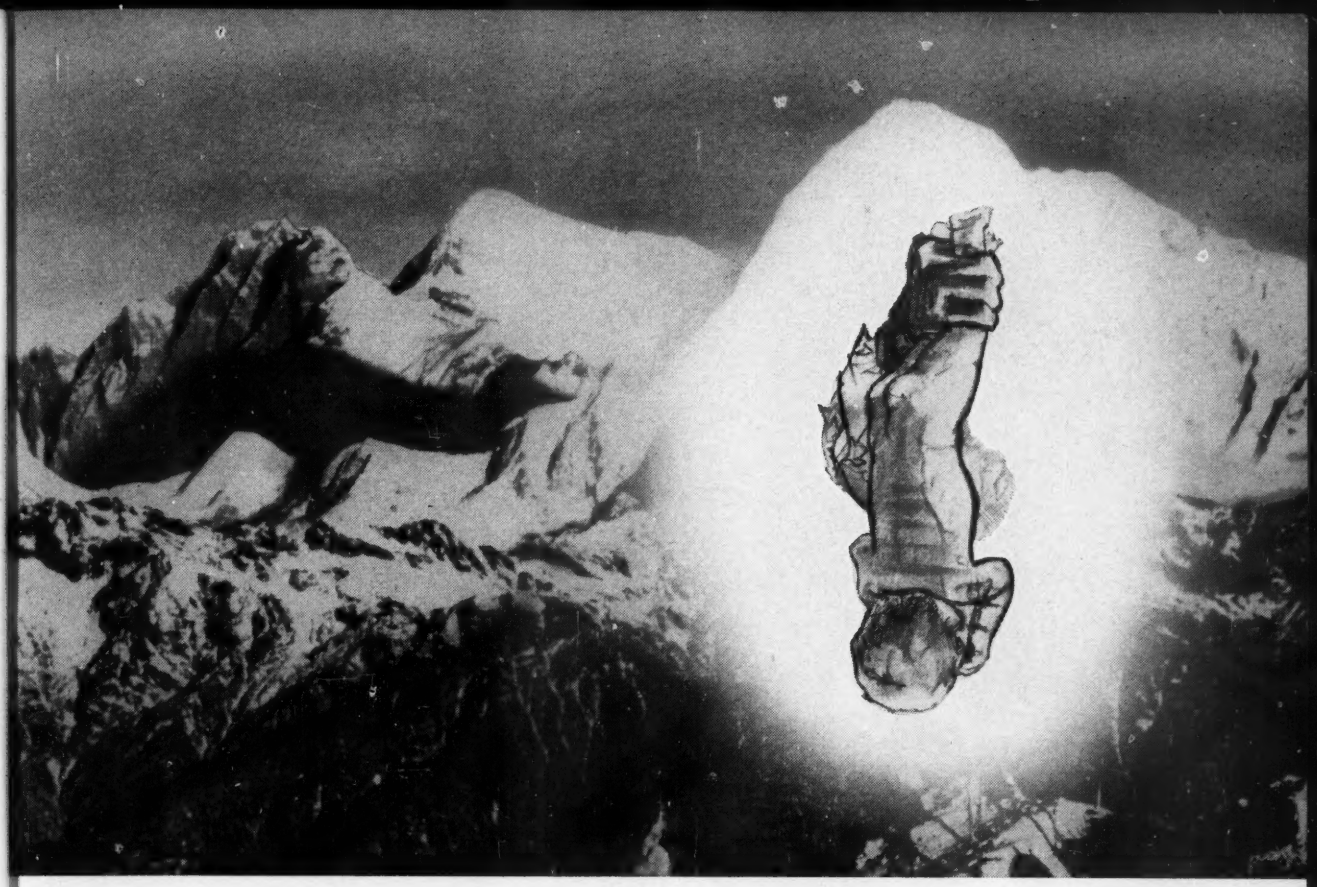
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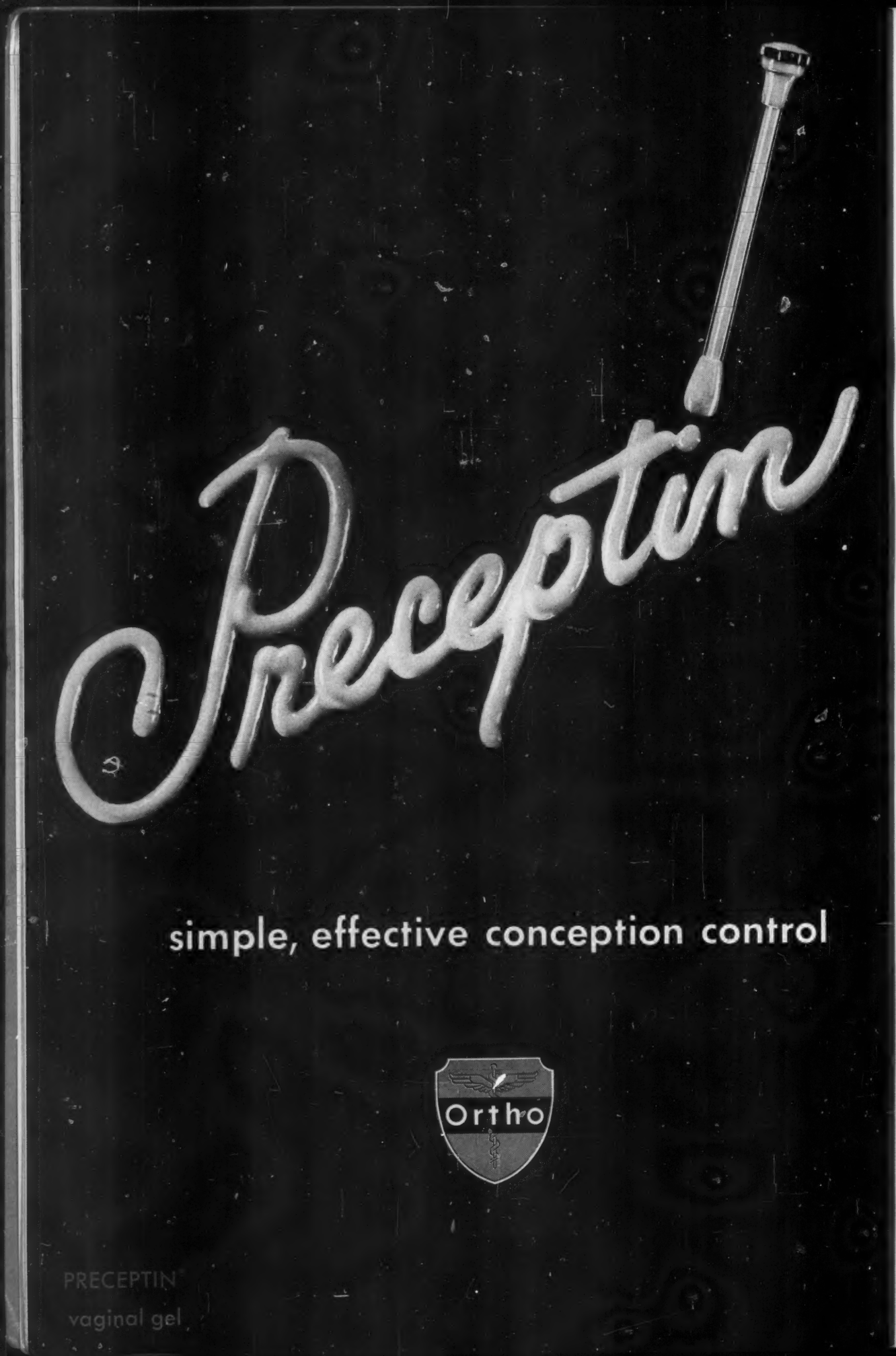
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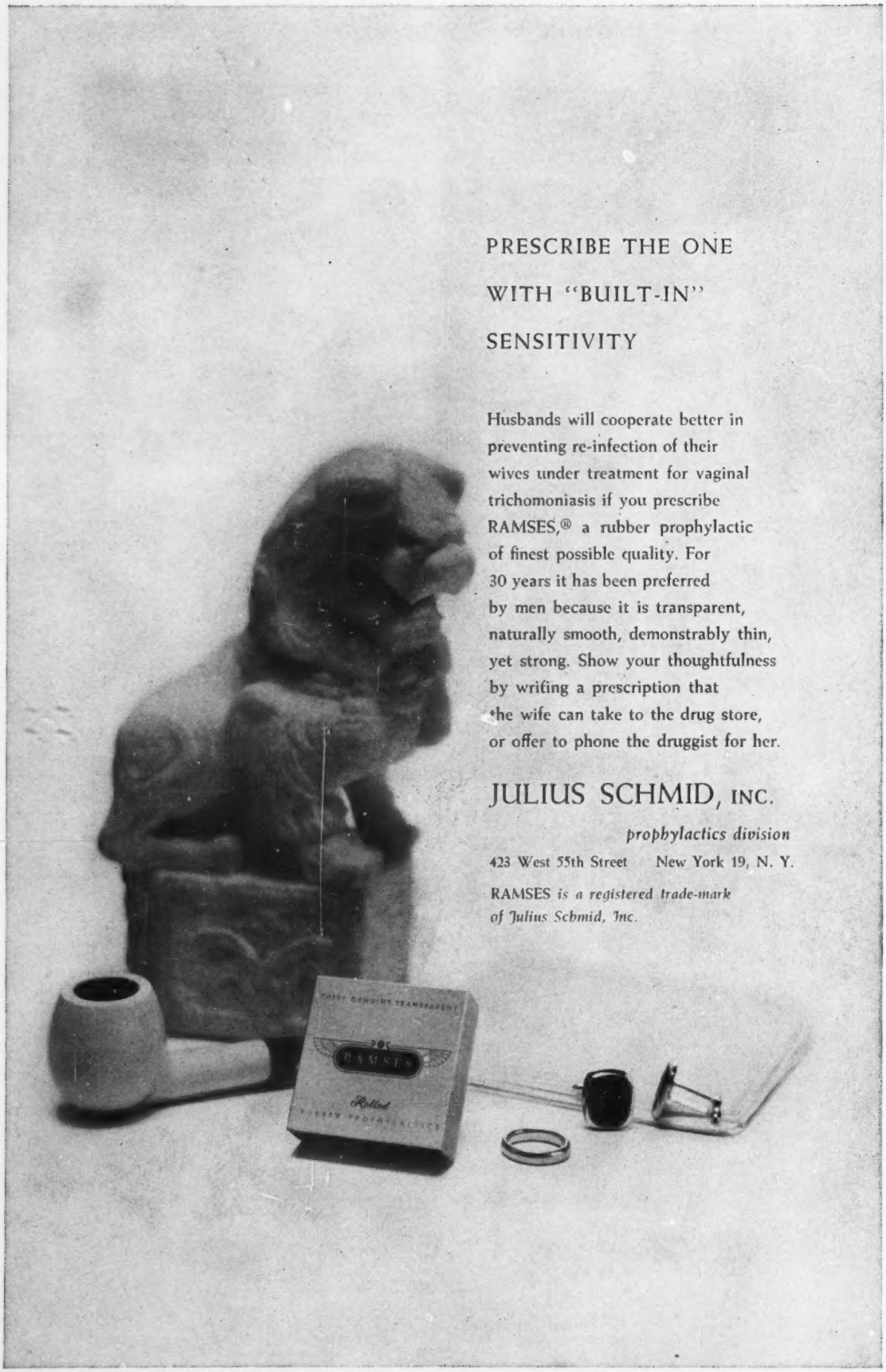
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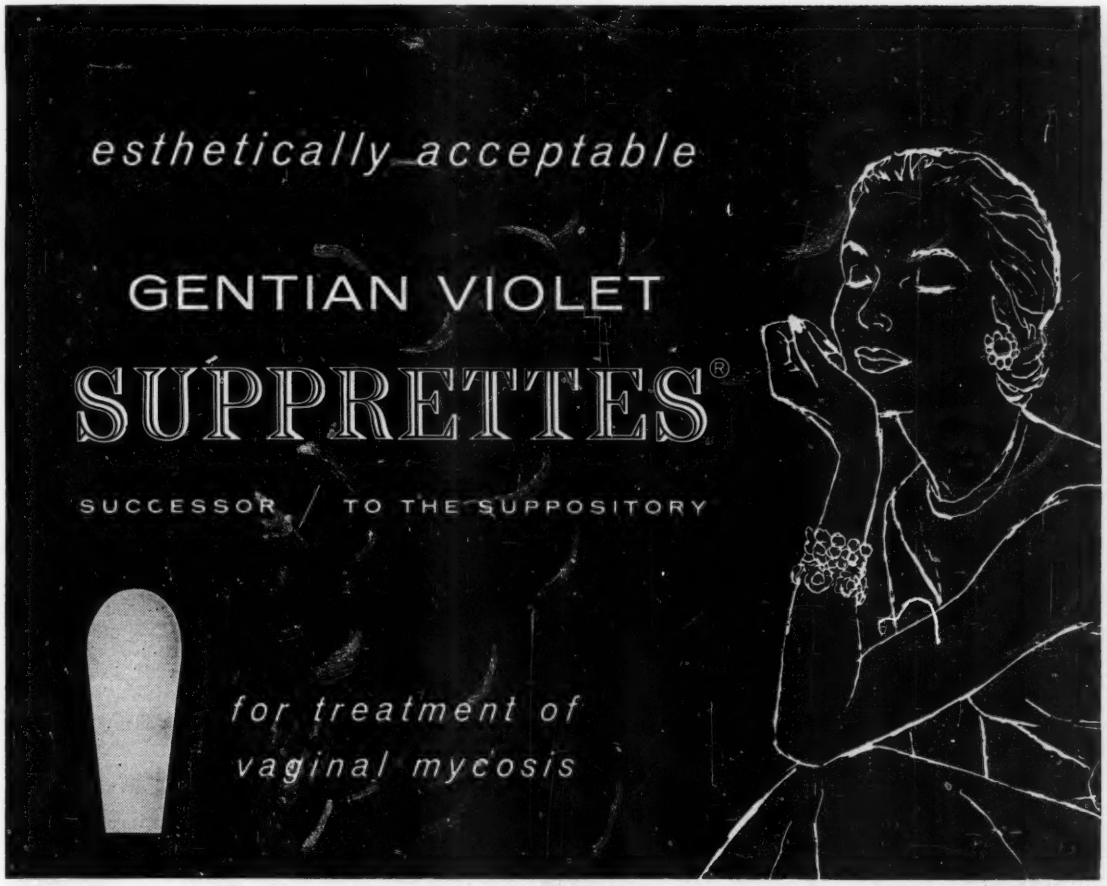
Husbands will cooperate better in preventing re-infection of their wives under treatment for vaginal trichomoniasis if you prescribe RAMSES,® a rubber prophylactic of finest possible quality. For 30 years it has been preferred by men because it is transparent, naturally smooth, demonstrably thin, yet strong. Show your thoughtfulness by writing a prescription that the wife can take to the drug store, or offer to phone the druggist for her.

JULIUS SCHMID, INC.

prophylactics division

423 West 55th Street New York 19, N. Y.

RAMSES *is a registered trade-mark of Julius Schmid, Inc.*



Gentian Violet Supprettes are preferred by physicians for maximum fungicidal activity . . . by patients for minimal messiness

Gentian Violet Supprettes provide rapid relief from itching, burning, and discharge without irritation to vaginal membranes. Effective even in resistant cases of monilial vaginitis. Messiness and cost are less than with other gentian violet preparations.

Composition: Each Supprette contains gentian violet 0.2%, lactic acid 0.3%, and acetic acid 1.0%.
Supplied: In jars of 12.

- Pregnancy moniliasis
- Antibiotic moniliasis
- Mycotic leukorrhea
- Diabetic vulvitis
- Mycotic vulvovaginitis
- Pruritus vulvae

The "Neocera" Base Makes the Difference

Contains no oils or fatty materials. Consists of water-soluble Carbowaxes* with active dispersal agent. Mixes completely with vaginal and cervical fluids to assure thorough penetration into folds of vaginal wall.

*Trademark U.C.C.

GENTIAN VIOLET SUPPRETTES

NO REFRIGERATION NECESSARY • Samples on Request

Webster **THE WILLIAM A. WEBSTER COMPANY • MEMPHIS 5, TENNESSEE**

In Madrid, too, you'll find Pentothal in constant use . . .



contributing to . . . a world-wide acceptance unmatched in modern intravenous anesthesia

Twenty years of use, over 2500 published reports—seldom in history of medicine has a single drug enjoyed the acceptance accorded Pentothal Sodium. This modern intravenous anesthetic is more than just thiopental sodium. It is thiopental sodium *plus* the most exacting controls . . . *plus* adaptability to widely varying practices . . . *plus* the most thoughtfully planned dosage forms. *Priceless pluses,* these, making Pentothal Sodium an agent of choice the world over in intravenous anesthesia. Abbott

PENTOTHAL® Sodium

(Thiopental Sodium for Injection, Abbott)

701056



NOW—the unequalled advantages of K_1—orally

Tablets

MEPHYTON®

(VITAMIN K_1, MERCK)

". . . vitamin K_1 is more effective than any other agent now available in combating drug-induced hypoprothrombinemia."[1] "Vitamin K_1 appears to be equally effective by the oral or intravenous route."[2] Beneficial effects are apparent in 6 to 10 hours following oral use.

Supplied: Oral MEPHYTON—tablets of 5 mg. of vitamin K_1, in bottles of 100. Emulsion of MEPHYTON—in boxes of six 1-cc. ampuls, 50 mg. of K_1 per cc.

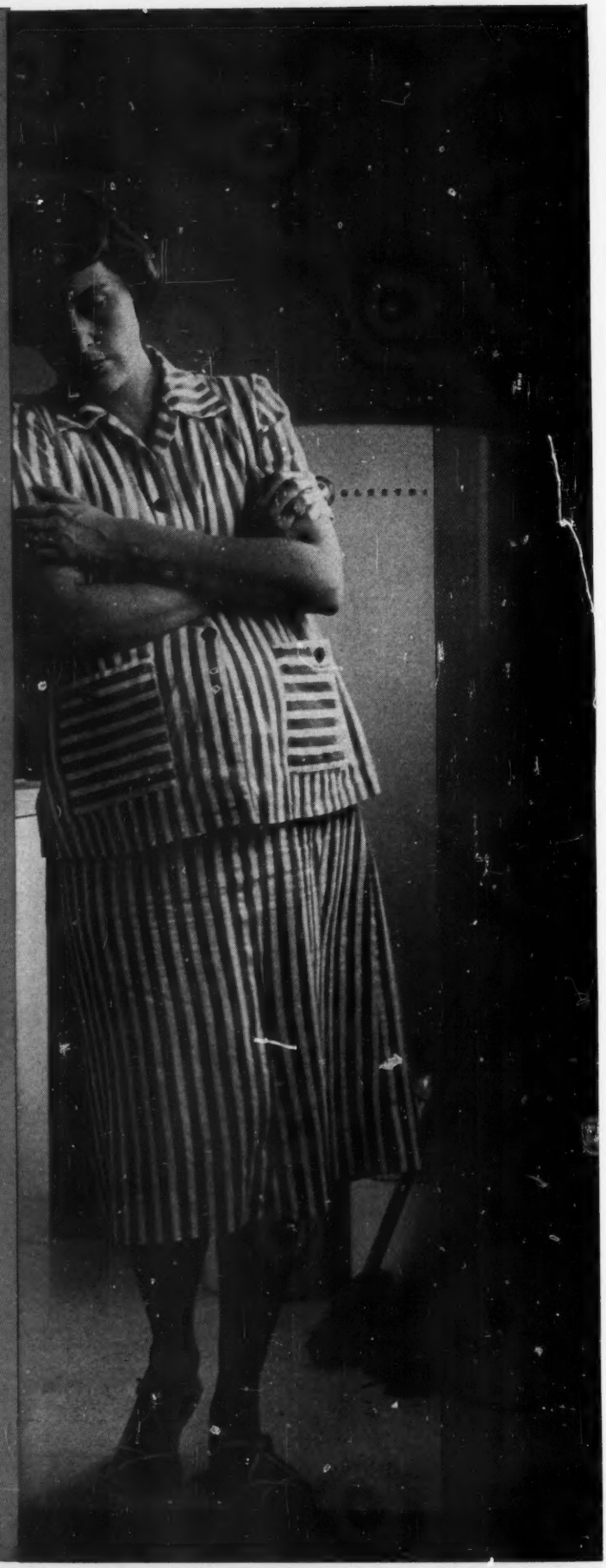
References: 1. Gamble, J.R., et al. Arch. Int. Med. **95**:52, 1955. 2. Gamble, J.R., et al. J. Lab. & Clin. Med. **42**:805, 1953.

MSD

MERCK SHARP & DOHME

DIVISION OF MERCK & CO., INC. PHILADELPHIA 1, PA.

You could help her enjoy pregnancy



'Dexamyl' smoothly and subtly helps to relieve lethargy and chronic fatigue. The elevation of mood and sense of well-being provided by 'Dexamyl' can help her to plan and accomplish her daily tasks.

Dexamyl*

tablets · elixir
Spansule† capsules

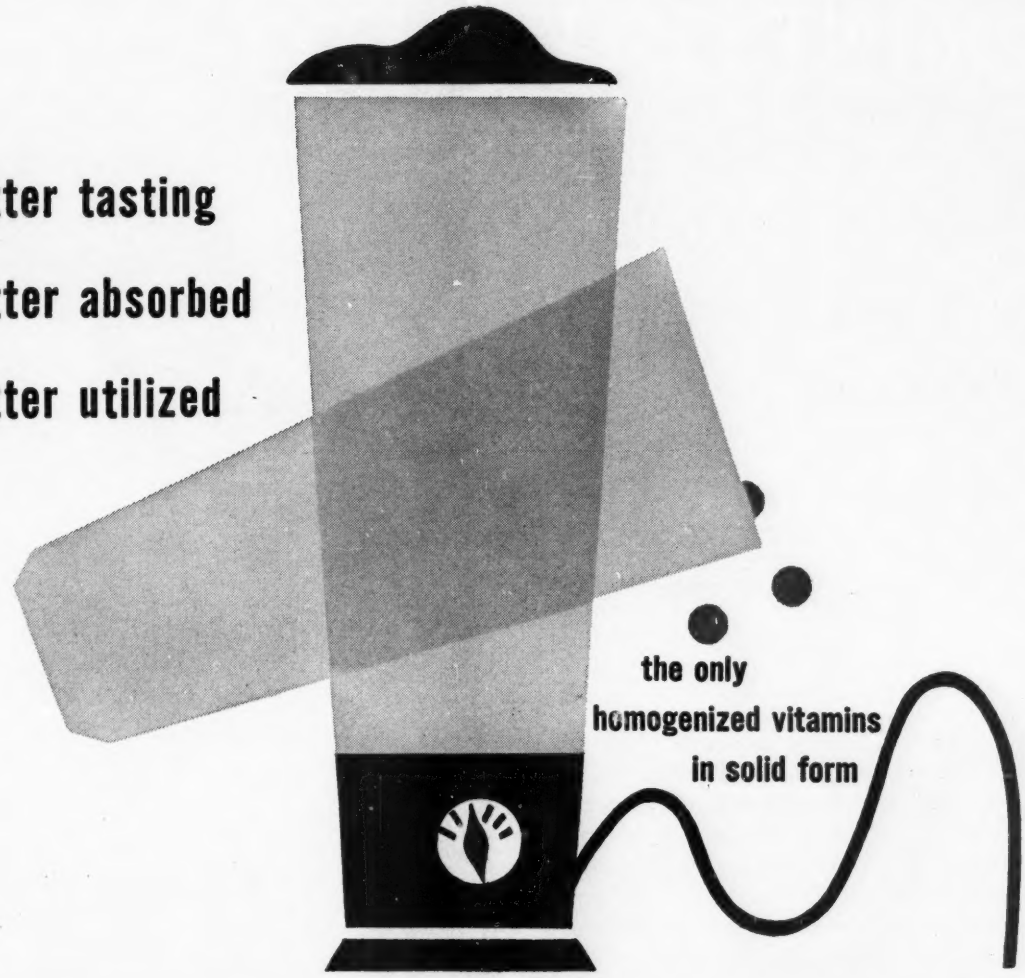
Smith, Kline & French Laboratories, Philadelphia

*T.M. Reg. U.S. Pat. Off.
†T.M. Reg. U.S. Pat. Off. for sustained release capsules, S.K.F.

better tasting

better absorbed

better utilized



HOMAGENETS®*

Homagenets provide multivitamins in the same way as do the most nutritious foods. By a unique process, the vitamins are homogenized, then fused into a solid, highly palatable form. Compare the taste of Homagenets with other vitamin preparations.

Homogenization presents both oil and water soluble vitamins in microscopic particles. This permits greater dispersion of the vitamins—thus better absorption and utilization. And the flavorful base assures patient acceptance.

*U.S. Pat. 2676136. Other Pat. Pending

Advantages—

Better absorption, better utilization

Excess vitamin dosage unnecessary

Pleasant, candy-like flavor

No regurgitation, no "fishy burp"

May be chewed, swallowed or dissolved in the mouth

Three formulas:

Prenatal Pediatric Therapeutic

Send for samples of Homagenets. Taste them, and compare.

The S. E. MASSENGILL Company

BRISTOL, TENNESSEE • NEW YORK • KANSAS CITY • SAN FRANCISCO

postpartum pain

effectively controlled for 10 to 12 hours on a single tablet



For the first time you can now prescribe extended action codeine. Donnagesic *Extentabs* offer the obstetrician the high level of codeine analgesia he needs[1,2] to help give a restful puerperium to the 75 per cent of multiparas who suffer after-pains.[1]

But more than extended codeine analgesia is provided by Donnagesic. Essential sedation[1,3] to reduce pain consciousness and anxiety is also provided, for Donnagesic contains the balanced ratio of natural belladonna alkaloids and phenobarbital of Donnatal®

Further, the phenobarbital augments the potent analgesia provided,[4] while the alkaloids minimize the possibility of codeine constipation, nausea and vomiting, which occasionally result from codeine administration.

DONNAGESIC	No. 1 (pink)	No. 2 (red)
CODEINE Phosphate	48.6 mg. (¾ gr.)	97.2 mg. (1½ gr.)
Hyoscyamine Sulfate ...	0.3111 mg.	0.3111 mg.
Atropine Sulfate	0.0582 mg.	0.0582 mg.
Hyoscine Hydrobromide..	0.0195 mg.	0.0195 mg.
Phenobarbital	48.6 mg. (¾ gr.)	48.6 mg. (¾ gr.)

Dosage: One or two Donnagesic Extentabs No. 1 or No. 2 every 10 to 12 hours.

Extended Action: The intensity of effects smoothly sustained ALL-DAY or ALL-NIGHT by each Donnagesic *Extentab* is equivalent to, or greater than, the maximum which would be provided by q.4h administration of one-third the ingredients stated in the formula.

1. DeLee, J. B., and Greenhill, J. P.: Principles and Practice of Obstetrics, Philadelphia, W. B. Saunders Company, 1948; p. 399.
2. Williams, W. J.: Obstetrics, Eastman, N. J. (ed.), New York, Appleton-Century-Crofts, Inc., 1950; p. 457.
3. Beck, A. C.: Obstetrical Practice, Baltimore, The Williams and Wilkins Company, 1947; p. 332.
4. Goodman, L. S., and Gilman, A.: The Pharmacologic Basis of Therapeutics, N. Y., The Macmillan Company, 1955; p. 127.

A. H. ROBINS CO., INC., Richmond 20, Virginia *Ethical Pharmaceuticals of Merit Since 1878*

Robins

Donnagesic Extentabs

Extended action tablets of Codeine with Donnatal®

no call from pain tonight



Romilar
'Roche'
relieves cough—

...specifically,
by direct suppression
of the cough reflex.
But unlike narcotics,
Romilar does not cause
central depression,
drowsiness, constipation,
or other side effects.
Available as syrup,
tablets, and expectorant
(c NH_4Cl).

Romilar® HBr – brand of dextromethorphan HBr

in a single tablet —

pain relief
plus
antibacterial action

AZO GANTRISIN

In urinary tract infections, Azo Gantrisin usually provides effective antibacterial control (local and systemic), together with prompt relief of associated pain and discomfort . . . by combining well-tolerated Gantrisin with a clinically proved urinary analgesic.

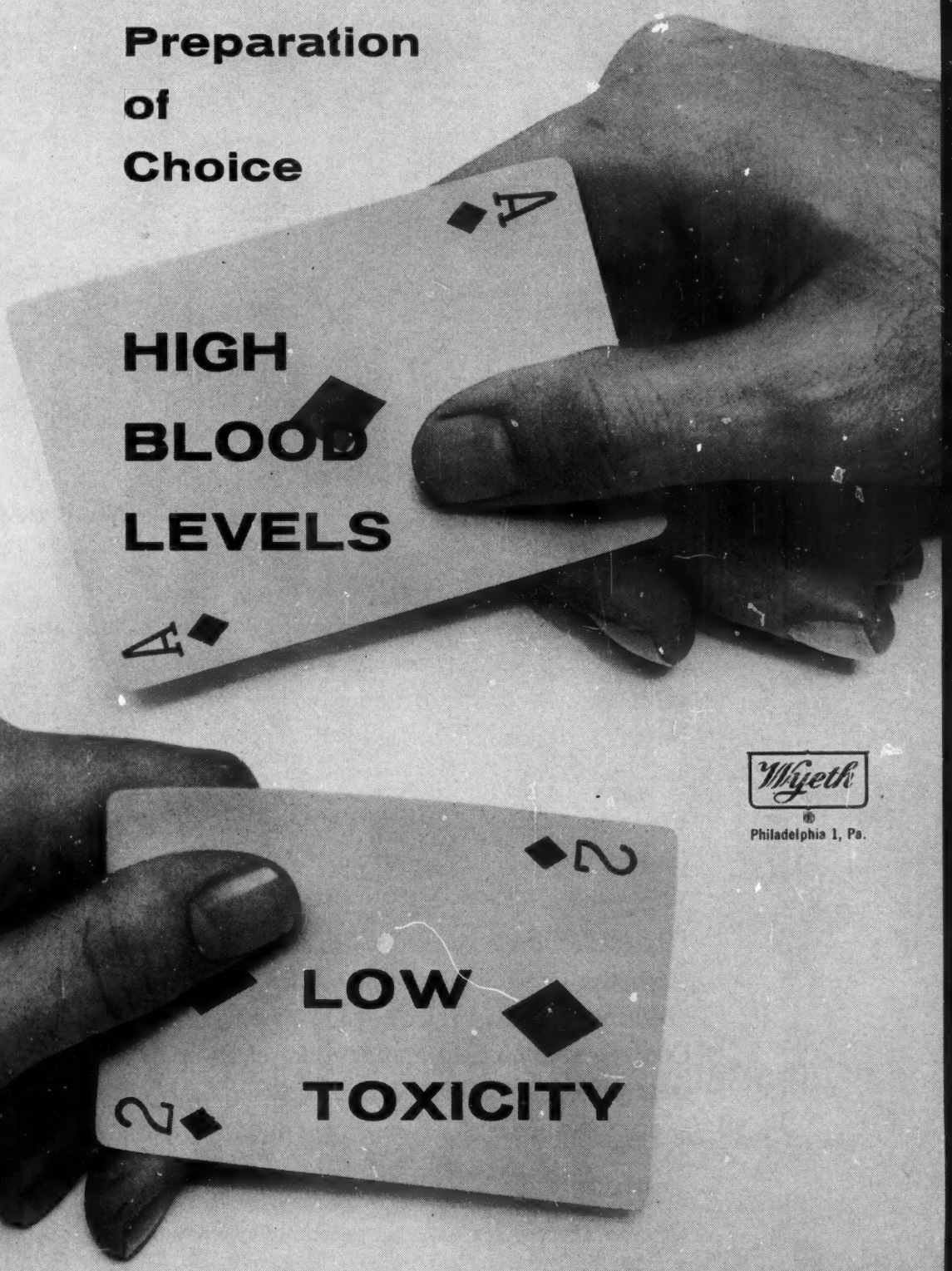
ROCHE

Each Azo Gantrisin tablet contains 0.5 Gm Gantrisin 'Roche' plus 50 mg phenylazo-diamino-pyridine HCl.

Gantrisin® - brand of sulfisoxazole

In Urinary-Tract Infections

Preparation of Choice

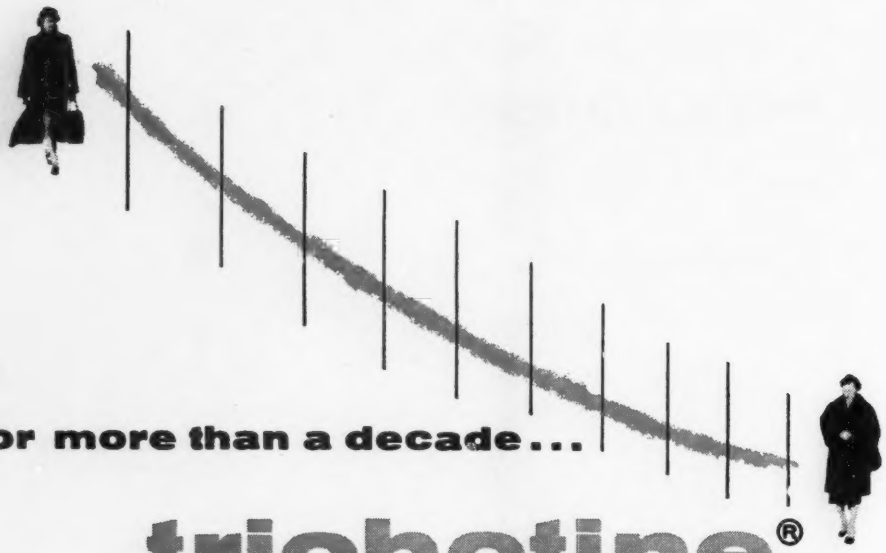


Wyeth
Philadelphia 1, Pa.

SUSPENSION TABLETS

SULFOSE®

Triple Sulfonamides
(Sulfadiazine, Sulfamerazine, Sulfamethazine)



for more than a decade...

trichotine®

...proved effective in vulvovaginal therapy

Trichotine—more than a decade ago—pioneered in newer, more effective vulvovaginal therapy by combining the multiple advantages of sodium lauryl sulphate with the recognized values of such specific or adjunctive agents as sodium perborate, sodium borate, thymol, eucalyptol, menthol and methyl salicylate.

Extensive clinical experience has proved its efficacy in trichomonas vaginalis vaginitis, subacute and chronic cervicitis, vulvovaginal moniliasis, non-specific leukorrhea, and pruritus vulvae.

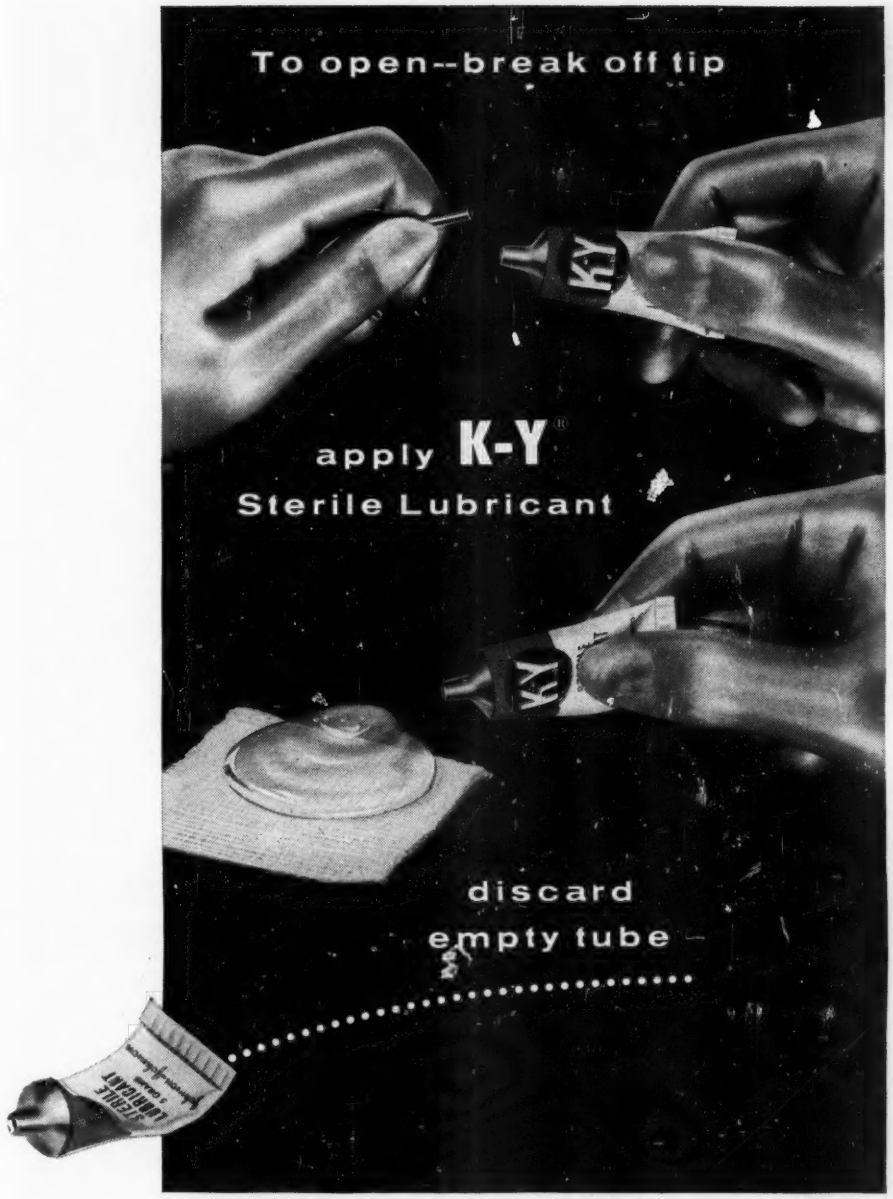
Trichotine douches may be prescribed as often as indicated—excellent also for postmenstrual or postcoital hygiene. Concentrated solutions are useful for clean-up or swab treatments in office. Hot packs are often quickly effective in pruritus vulvae.

A DETERGENT · A BACTERICIDE AND FUNGICIDE · AN ANTIPRURITIC

AN AID TO EPITHELIZATION · AN AESTHETIC AND PSYCHOSOMATIC ADJUNCT

Sample and literature on request *Available in jars of 5, 12 and 20 oz.*

the fesler co., inc., 375 Fairfield Ave., Stamford, Conn.



new single-use K-Y Sterile Lubricant

guarantees a sterile jelly for each application. No lost caps . . . no contamination.

ANOTHER QUALITY PRODUCT FROM THE RESEARCH LABORATORIES OF

Johnson & Johnson

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Pre-cauterization



2 weeks post-cauterization



3 weeks post-cauterization, healing nearly complete

PHOTOGRAPHS BY SCHWARTZ, J.: AM. J. OBST. 63:579, 1952.



FACILITATE HEALING

after electrosurgery for cervicitis in cancer prevention

There is a "... wealth of statistical proof that chronic cervicitis is an important predisposing factor in the development of cervical carcinoma ..."[1]:

No. cases cervicitis	Treatment	Developed cancer	Followed
1,000	wide conization	0	2-14 years
1,408	cauterization	0	3 years
2,985	cauterization or diathermy	0	10 years
1,150	cauterization	0	not stated[1]

Electrosurgery is treatment of choice in long-standing cervicitis.[2] When purulent discharge and inflammation are present, treat with FURACIN Vaginal Suppositories before electrocautery.[3] Afterward, use them to prevent infection and accelerate healing.[4]

FURACIN VAGINAL SUPPOSITORIES facilitate healing by control of surface infection. They form a lasting bactericidal coating over cervix and vagina. Effective in blood, pus and vaginal debris. Nontoxic to healing tissue. No staining or leakage. Safe for prolonged use.

PRESCRIBE FOR: leukorrhea of bacterial vaginitis • infected cervical erosions; before and after cervicovaginal surgery[4] and pelvic radiation[5].

FORMULA: 0.2% FURACIN in water-miscible base; hermetically sealed in yellow foil.

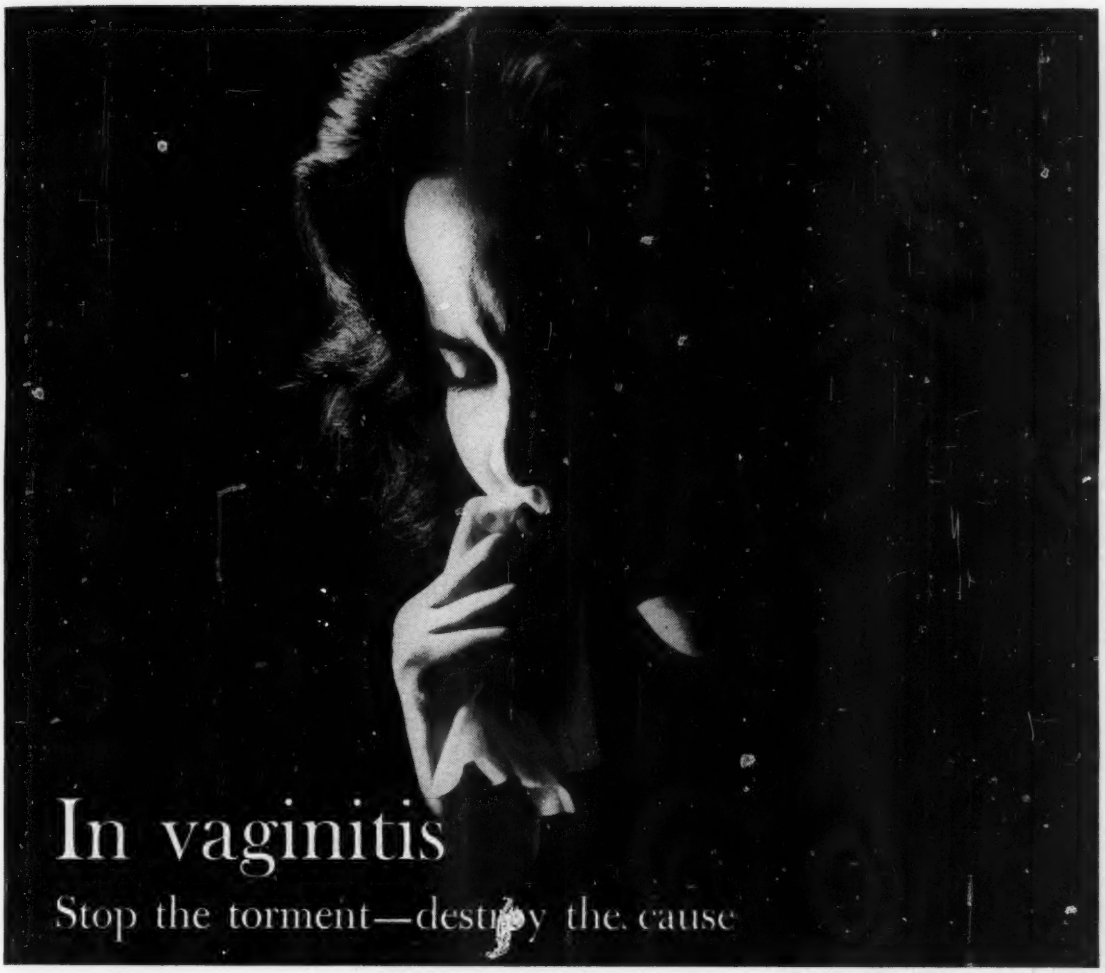
1. Crossen, R. J.: Diseases of Women, St. Louis, the C. V. Mosby Company, 1953, p. 509. 2. Novak, E., and Novak, E. R.: Textbook of Gynecology, Baltimore, The Williams and Wilkins Company, 1952, p. 220. 3. Patterson, J. F., Jr.: North Carolina M. J. 17:165, 1956. 4. Schwartz, J.: Am. J. Obst. 63:579, 1952. 5. Schwartz, J., and Nardiello, V.: Am. J. Obst. 65:1069, 1953.

FURACIN® VAGINAL suppositories

BRAND OF NITROFURAZONE

EATON LABORATORIES
Norwich New York

NITROFURANS
a *new* class of antimicrobials
neither antibiotics nor sulfonamides



AVC

Improved



in trichomonal vaginitis –
"... the most effective treatment available."[1]



in monilial vaginitis –
"... more effective than any other agent ... used previously."[2]



in mixed infection –
"... the most effective treatment of endocervicitis. ..."[3]

The rate of cure with AVC Improved is consistently high in all common types of vaginitis. In one series of patients with trichomonal vaginitis, bacteriologic cures were obtained in 82.5% of the cases.[1] Symptomatic relief is rapid and lasting. And because AVC Improved has an acid pH, it encourages the early return of normal vaginal flora.

Composition: A nonstaining cream containing 9-aminoacridine hydrochloride 0.2%; sulfanilamide 15.0%; allantoin 2.0%; with lactose in a water-miscible base buffered to pH 4.5.

Indications: Trichomonal leukorrhea; monilial and nonspecific vaginitis; cervicitis; postpartum hygiene; pre- and postcauterization, coagulation, conization, and other vaginal surgery; vaginal infections in children.

Administration: An applicatorful twice daily—on arising and at bedtime.

Supplied: 4 oz. tubes with or without applicator.

(1) Cortese, J. T.: Clin. Med. *2*:45, 1955. (2) Hensel, H. A.: Postgrad. Med. *8*:293, 1950. (3) Horoschak, A. and Horoschak, S.: J. M. Soc. New Jersey *43*:92, 1946.

Products of Original Research

THE NATIONAL DRUG COMPANY
Philadelphia 44, Pa.

I've Got a Secret



It's probably that he has a frog in his pocket... but his mother also has a secret... she's going to have a baby.

This intelligent modern mother has placed herself in the care of the physician in whom she has implicit faith. Now, the Doctor may, and probably does, prescribe a number of different prenatal supplements to his patients for various but valid reasons.

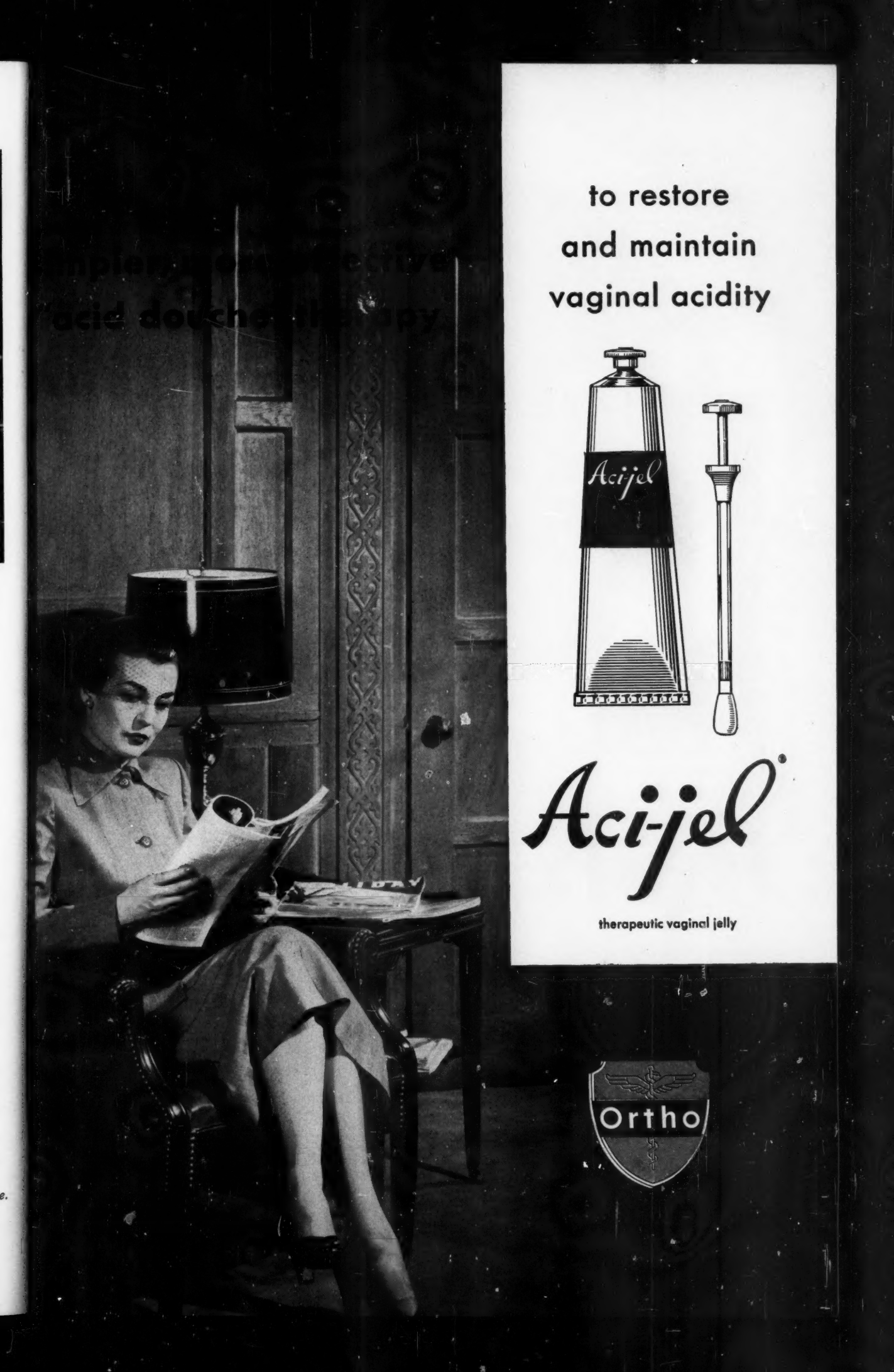
It is quite possible, indeed probable, that the physician may consider the use of a phosphorus-free, aluminum hydroxide containing product. Especially if it also provides organic iron, Vitamin B12 with intrinsic factor, plus the *important* vitamins in the *new* levels suggested for pregnant or lactating women. There are only a very *few* such quality formulas available for his choice.

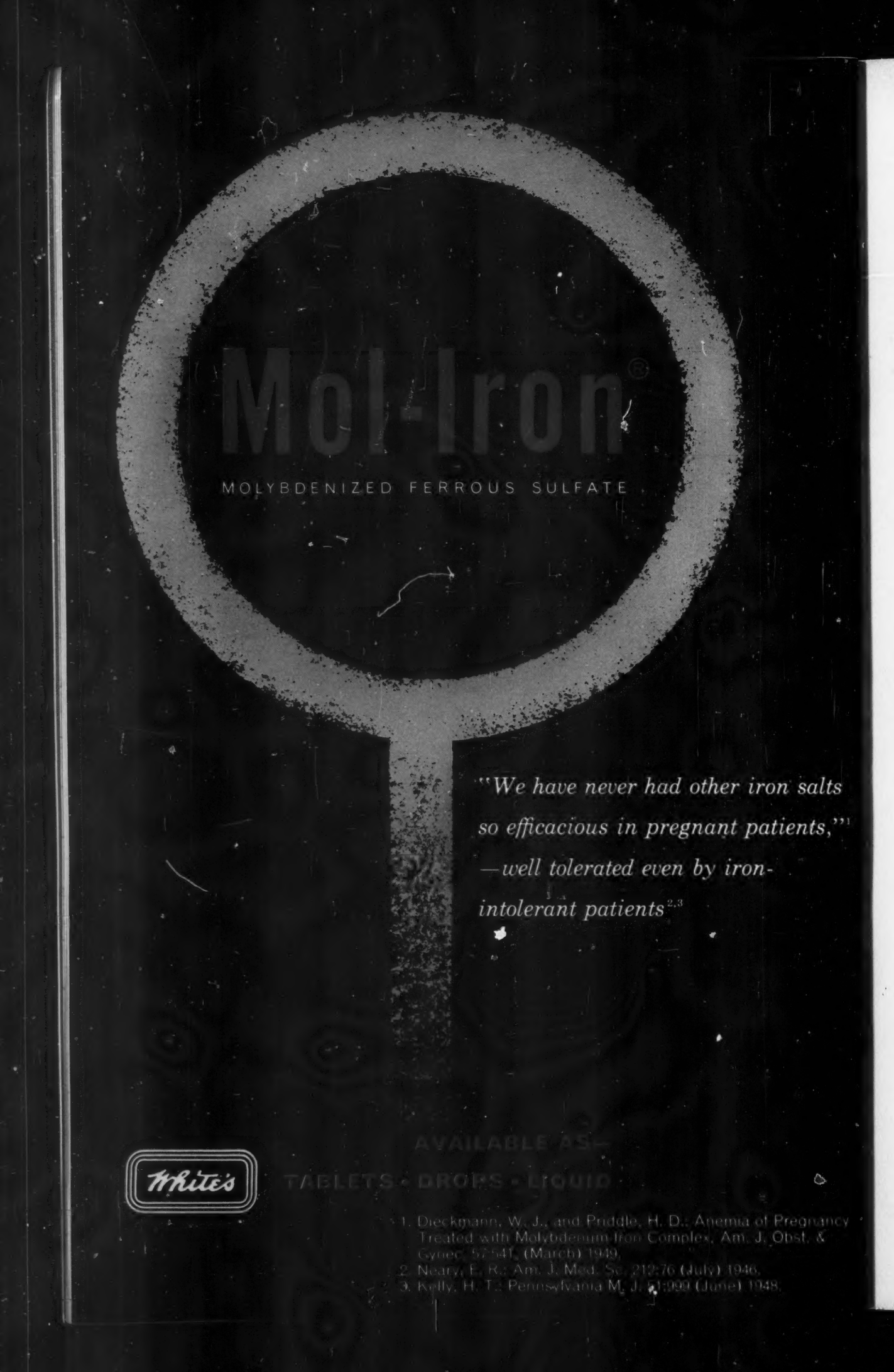
One such formula with perhaps the easiest product name to remember on the national scene is Calcinatal ® *(pronounced Calci' natal)* by Nion.

Patient acceptance of these easy-to-swallow tablets (not capsules) is quite understandable. Incidentally, one of your obstetrical problems, "control of Cramps" will be relegated to one of very minor incidence by use of the product. For more complete information, samples and brochure write to

NION CORPORATION
LOS ANGELES 38, CALIFORNIA

P.S. *We feel copy writers usually mention product names too often . . . . we mention ours but once. It is so easy to remember and hard to forget. Say it once – try to forget it.*


to restore
and maintain
vaginal acidity
Aci-jel
Aci-jel®
therapeutic vaginal jelly
Ortho



1. Dieckmann, W. J., and Priddle, H. D.: Anemia of Pregnancy Treated with Molybdenum-Iron Complex, Am. J. Obst. & Gynec. 57:541 (March) 1949.
2. Neary, E. R.: Am. J. Med. Sc. 212:76 (July) 1946.
3. Kelly, H. T.: Pennsylvania M. J. 51:999 (June) 1948.

the only

prenatal supplement

with **Mol-Iron**

Gestatabs® tablets

"just 2 for 2"

—for real patient convenience

only 2 tablets a day

Available in bottles of 60 tablets

PHOSPHORUS-FREE CALCIUM
to minimize the likelihood of leg cramps

VITAMIN K
to bolster prothrombin levels

ESSENTIAL VITAMINS
to maintain normal pregnancy

and when iron is the dominant need...

Mol-Iron with calcium and vitamin D

Available in bottles of 60 tablets

Safety First | in control of Nausea of Pregnancy

The first thought of every physician during the prenatal period is the safety of the patient.

The first choice of the physician for an agent to control nausea and vomiting will be EMETROL® when he considers the following advantages:

1. EMETROL does not contain barbiturates, bromides, antihistamine compounds, or any other drugs likely to induce untoward effects.
2. EMETROL has been shown to be effective in nausea and vomiting in controlled clinical studies.[1-3]
3. EMETROL is so palatable that most patients will take it readily.
4. EMETROL works quickly, often bringing relief with the first dose.

SAFE

EMETROL®

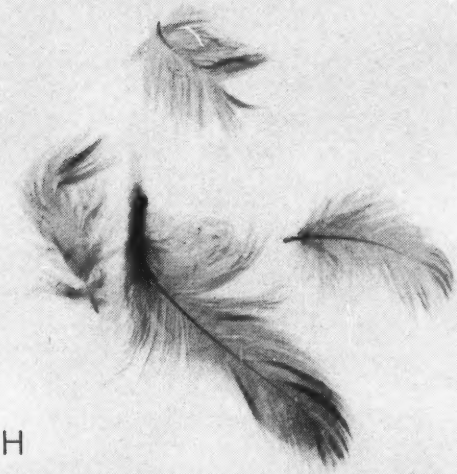
(Phosphorated Carbohydrate Solution)



1. Crunden, A. B., Jr., and Davis, W. A.: Am. J. Obst. & Gynec. 65:311, 1953.
2. Bradley, J. E., et al.: J. Pediat. 38:41, 1951.
3. Tebrock, H. E., and Fisher, M. M.: M. Times 82:271, 1954.

Kinney®

KINNEY & COMPANY, INC.
COLUMBUS, INDIANA



SURGEONS WITH

"THE FEATHER TOUCH"

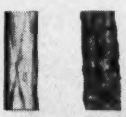
CHOOSE FINER SIZES OF D&G GUT

"Gentleness in handling fragile tissues must be mastered, and the feather touch is essential."

Potts, W. J.: J. A. M. A. 157:627 (Feb. 19) 1955, p. 629.

SURGEONS APPRECIATE the smooth flexible "hand" of D & G gut. They sense the extra knot security offered by D & G's special matte finish.

The rapid trend to the regular use of 000, 4-0 and 5-0 gut in the past five years has brought increased recognition of the values of D & G gut. Special processing assures the most strength with the least gut—unlike ordinary gut which is ground to size with some loss of flexibility and tensile strength.



D & G gut — other gut

The finer sizes of D & G plain, mild chromic and medium chromic gut are, and have been, the acknowledged world-wide standard for gastrointestinal and eye surgery for over twenty years.

When you want to approximate mucous membranes... repair tissues of the neck... ligate small blood vessels . . . or whenever you want to use your "feather touch," check with your O R Supervisor to be sure you have the advantages of finer sizes of D & G gut.

AMERICAN CYANAMID COMPANY
SURGICAL PRODUCTS DIVISION
DANBURY, CONNECTICUT

Advancing with surgery

ANNOUNCING...

BIOPAR® FORTÉ

TABLETS

containing non-inhibitory intrinsic factor

providing **"parenteral B_{12} therapy" in a tablet**



2 tablets a day provide the same rapid and intense hemopoietic response as that obtained from injectable B_{12}

Biopar Forté, a new development in oral vitamin B_{12} therapy, contains non-inhibitory intrinsic factor superior to the ordinary factor preparations. The non-inhibitory factor permits optimal absorption of vitamin B_{12} at therapeutic dosage levels. Thus, stated potency and actual hemopoietic potency are more nearly equal than in vitamin B_{12} products containing the ordinary intrinsic factor.

Biopar Forté is also useful as an aid to nutrition, appetite, growth and convalescence; to correct deficient intestinal absorption of vitamin B_{12} particularly in elderly patients; and to relieve minor muscle and nerve pains, especially of neuritic origin.

Each Biopar Forté tablet contains:
Vitamin B_{12} with Intrinsic Factor Concentrate (non-inhibitory) ½ U.S.P. Unit (Oral)*
Vitamin B_{12} (activity equivalent) 25 mcg.

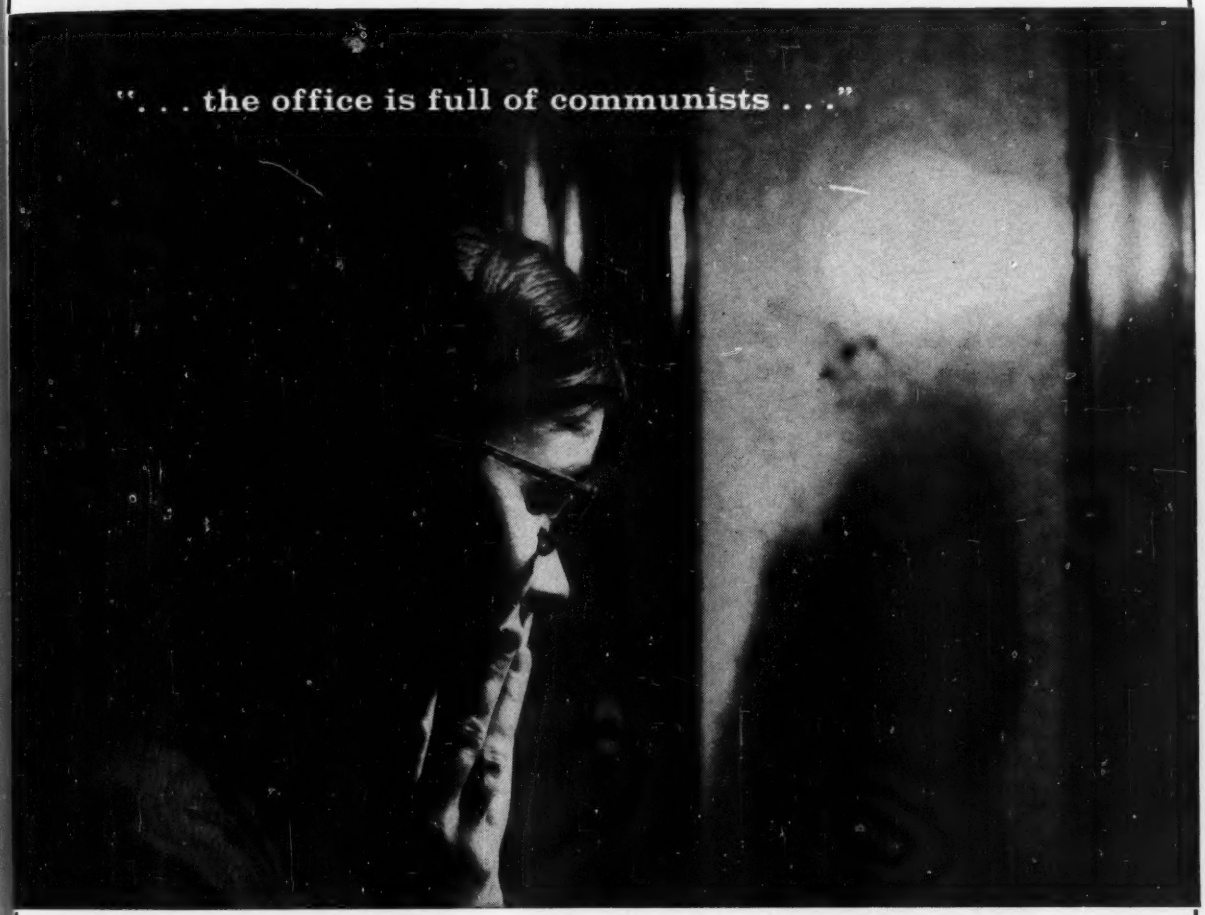
*Unitage established prior to compounding

Supply: Bottles of 30 tablets

Attention: Store in a cool place

THE ARMOUR LABORATORIES
A DIVISION OF ARMOUR AND COMPANY • KANKAKEE, ILLINOIS

'Thorazine' relieved this patient's severe anxiety and fear. She was able to continue working and soon began to gain insight.



'THORAZINE' CASE REPORT

patient: 29-year-old single female. Severe anxiety of two months' duration. Complained to police of car following her home nightly. Afraid to quit job because of fear of reprisal by communists in her office.

response: Intensity of symptoms diminished rapidly when 'Thorazine' was given. After one week, "remarks were no longer directed at communists." Patient quit her job and got a new one.

After three months of 'Thorazine' therapy, patient stated that she "felt fine" and her "work was very good." "Maybe it was my nerves and imagination, but that's behind me."

This case report is from the files of the patient's physician.

THORAZINE* one of the fundamental drugs in medicine

Smith, Kline & French Laboratories, Philadelphia

*T.M. Reg. U.S. Pat. Off. for chlorpromazine, S.K.F.



only pain is eliminated...

with HEAVY SOLUTION

Nupercaine®

When you provide saddle block anesthesia in obstetrical delivery, you assure "definite relief of pain . . . analgesia over the legs and thighs without causing paralysis of the muscles of the legs and thighs."[1]

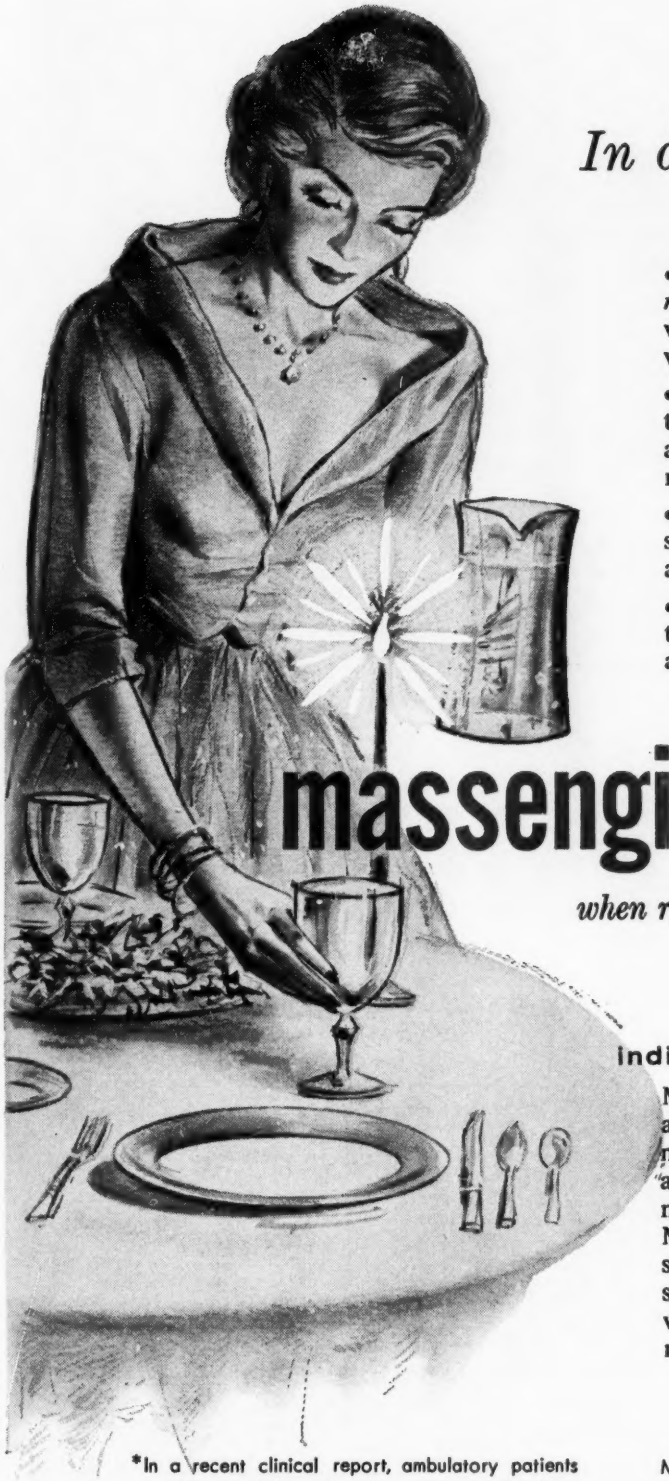
Supplied: 1:400 Nupercaine hydrochloride in 5% dextrose, 2-ml. ampuls, each ml. containing 2.5 mg. Nupercaine and 50 mg. dextrose; cartons of 10.

1. Causey, P. S., Reed, W. A., and Ford, J. L.: Arizona Med. *8*:27 (Dec.) 1951.

CIBA SUMMIT, N. J.

8/2189M

Heavy Solution Nupercaine® hydrochloride (dibucaine hydrochloride with dextrose 5% CIBA).



In deference to her daintiness...

- Massengill Powder is buffered to *maintain** an acid condition in the vaginal mucosa. It is more effective than vinegar and simple acid douches.
- Massengill Powder has a low surface tension which enables it to penetrate into and cleanse the folds of the vaginal mucosa.
- Massengill Powder has a "clean" antiseptic fragrance. It enjoys unusual patient acceptance.
- Massengill Powder solutions are easy to prepare. They are nonstaining, mildly astringent.

massengill powder®

when recommending a vaginal douche

Indications:

Massengill Powder solutions are a valuable adjunct in the management of monilia, trichomonas, staphylococcus, and streptococcus infections of the vaginal tract. Routine douching with Massengill Powder solution minimizes subjective discomfort and maintains a state of cleanliness and normal acidity without interfering with specific treatment.

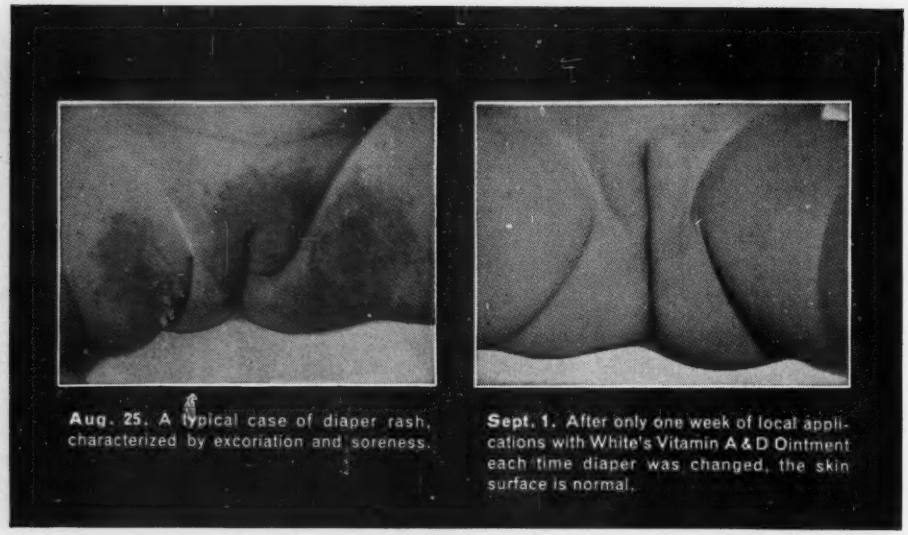
*In a recent clinical report, ambulatory patients —with an alkaline vaginal mucosa resulting from pathogens—maintained an acid vaginal mucosa of pH 3.5 for 4 to 6 hours after douching with Massengill Powder; recumbent patients maintained a satisfactory acid condition up to 24 hours.

*Arnot, P.H.: West. J. Surg., Obs., and Gyn. 62:85

Generous samples on request.

The S. E. MASSENGILL Company

Bristol, Tennessee New York Kansas City San Francisco



Aug. 25. A typical case of diaper rash, characterized by excoriation and soreness.

Sept. 1. After only one week of local applications with White's Vitamin A & D Ointment each time diaper was changed, the skin surface is normal.

it's becoming routine therapy

particularly in

prevention and treatment of diaper rash

and in many other common skin conditions: burns, cuts, sunburn, chafing, prickly heat, chapping, cracked nipples

White's Vitamin A & D Ointment

it's healing...soothing...protective.

Provides A & D vitamins in the same ratio as found in cod liver oil.

KEEP A TUBE OF THE NEW
ECONOMICAL 4 OZ. SIZE
HANDY FOR EMERGENCIES
AND ROUTINE SKIN CARE

WHITE LABORATORIES, INC.
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only the finest products bear this name

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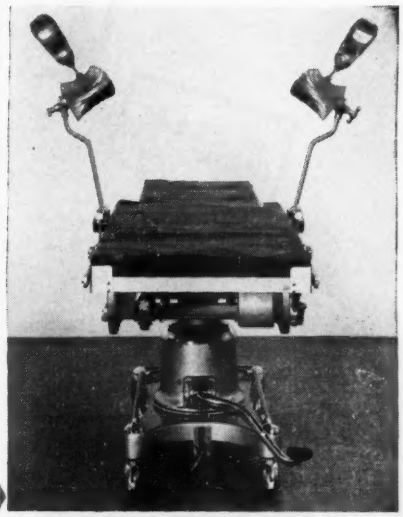
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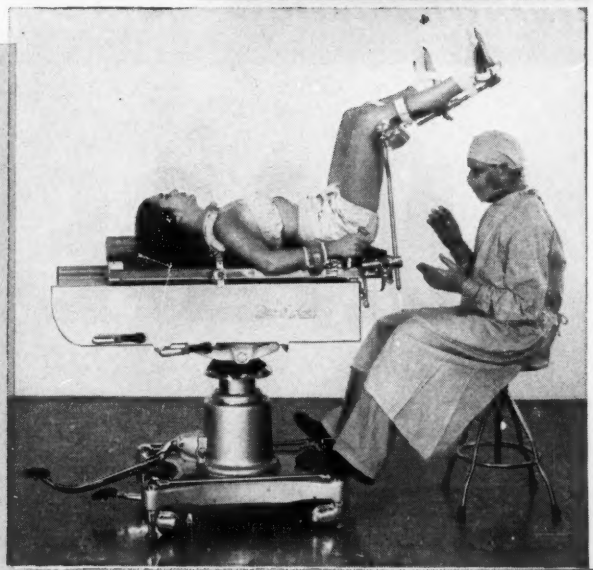
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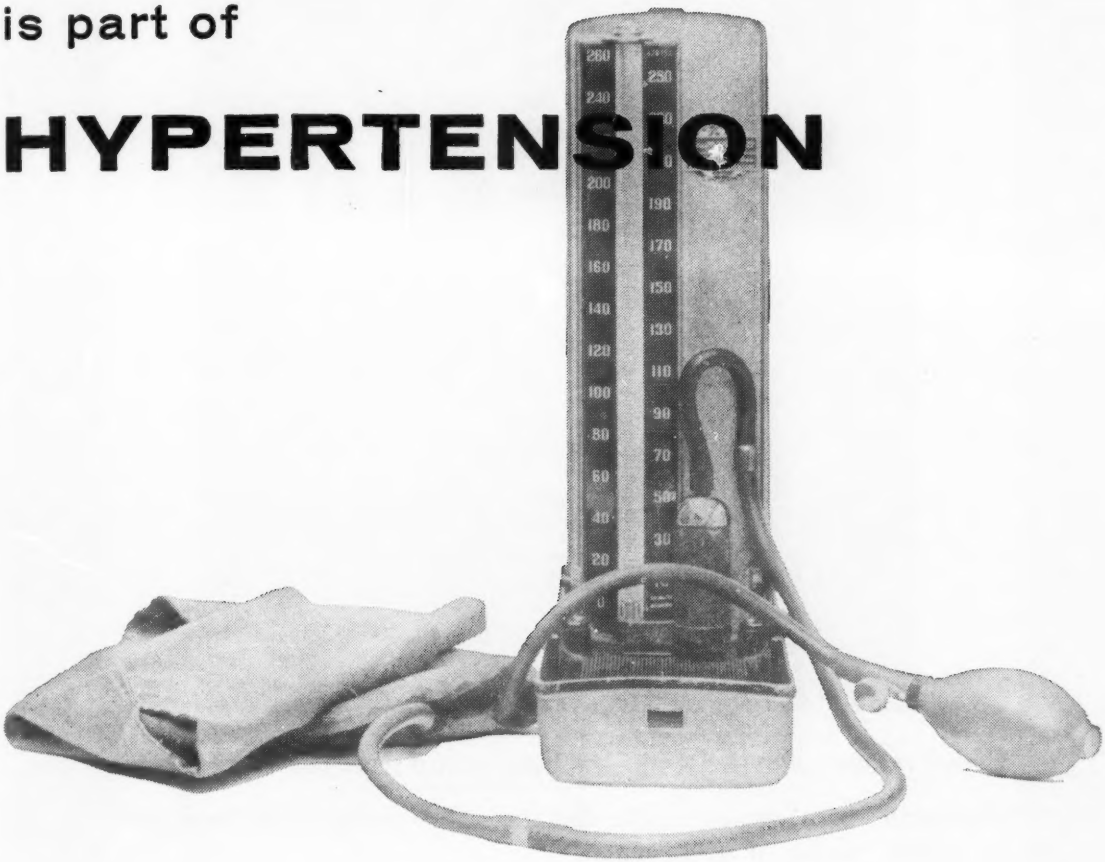
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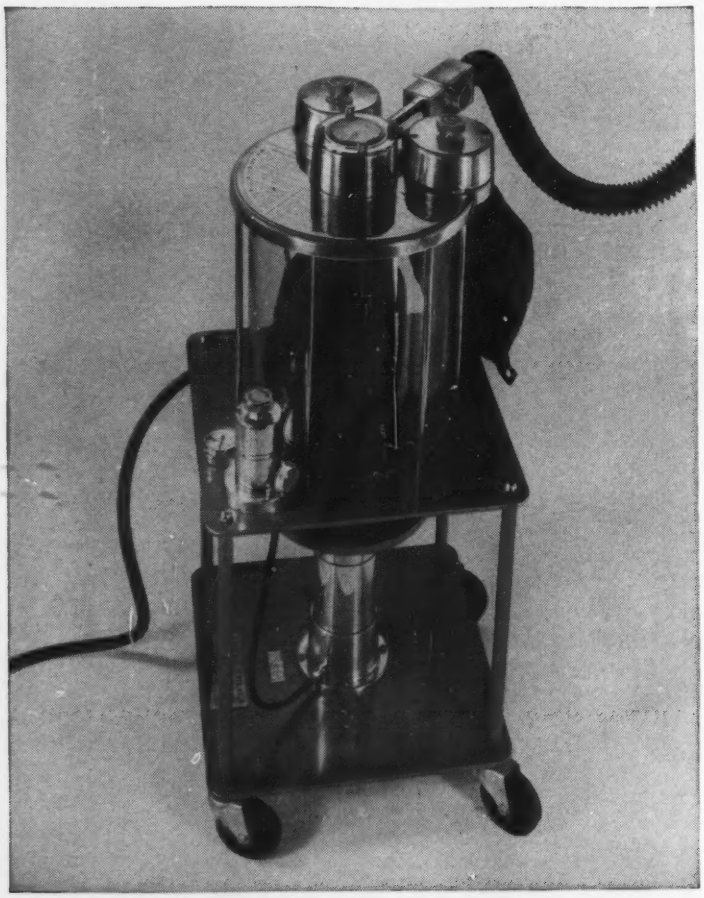
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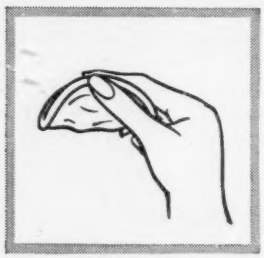


FIG. 1

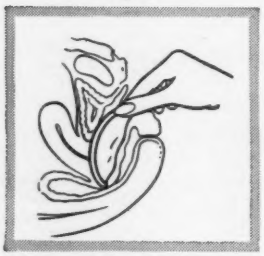


FIG. 2

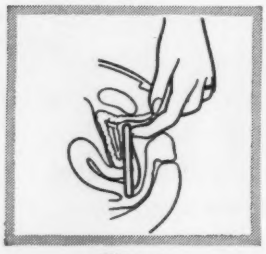


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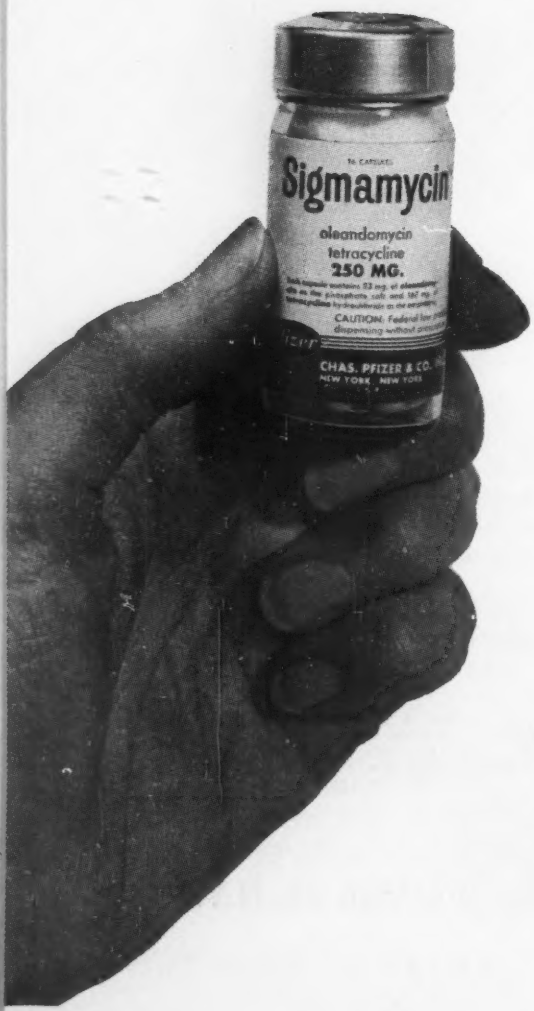
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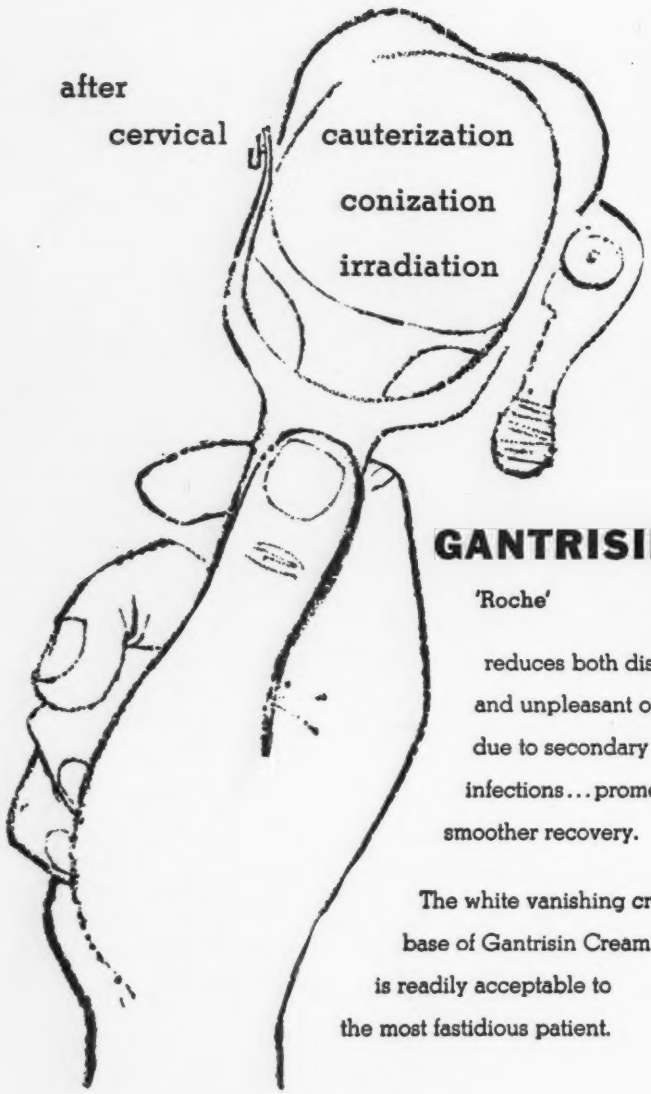
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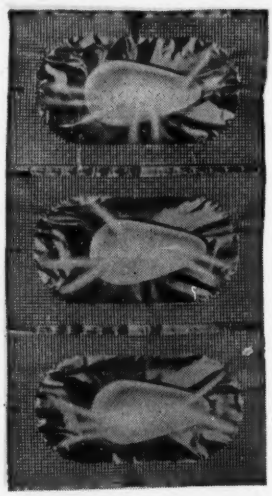
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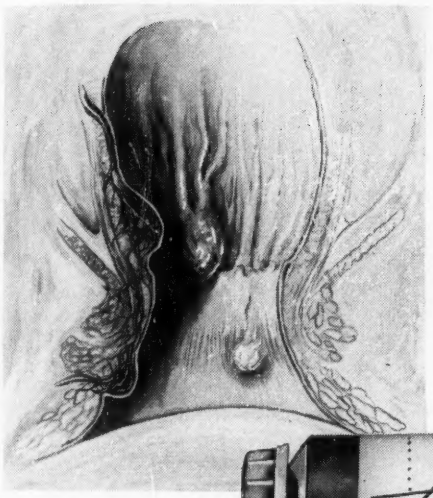
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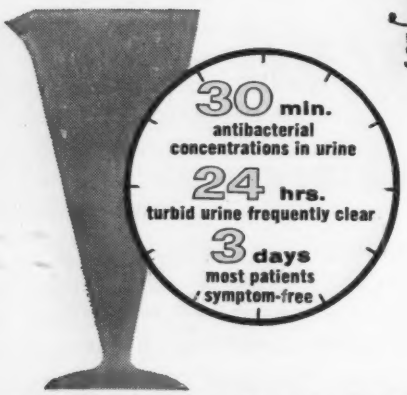
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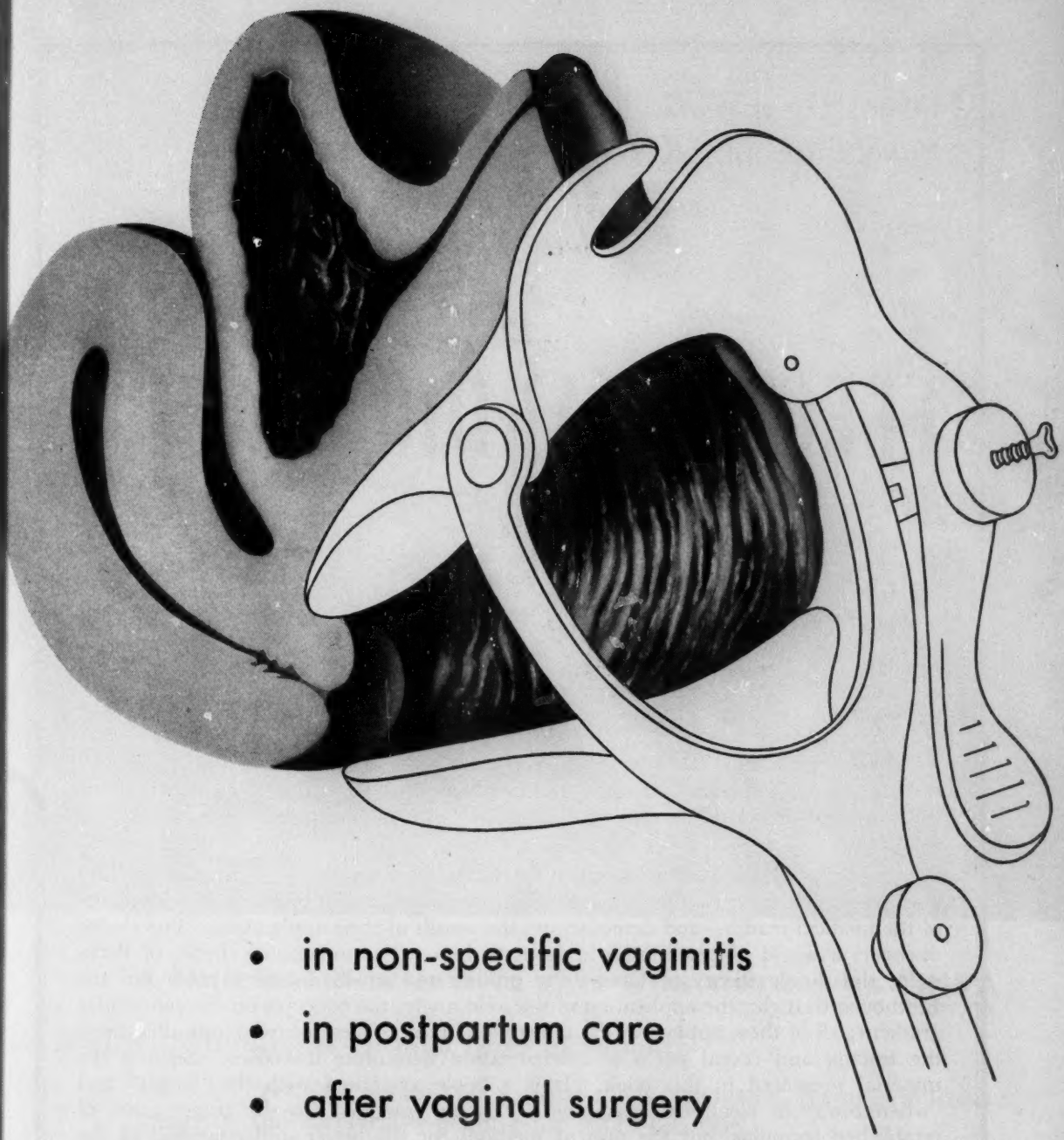
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*Stewart, B. L., and Rowe, H. J.: J. Am. M. Ass. **160**:1221, 1956.

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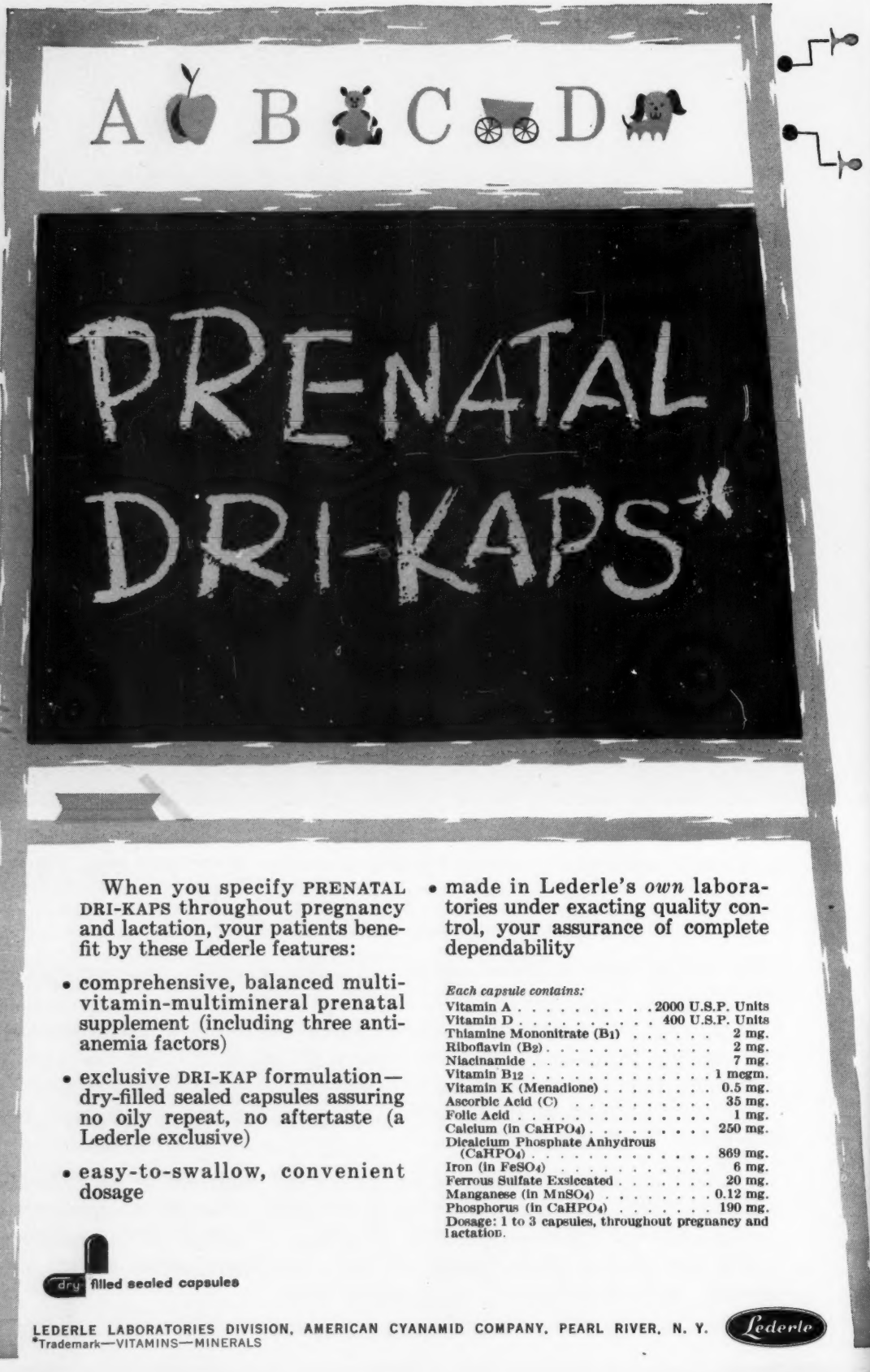
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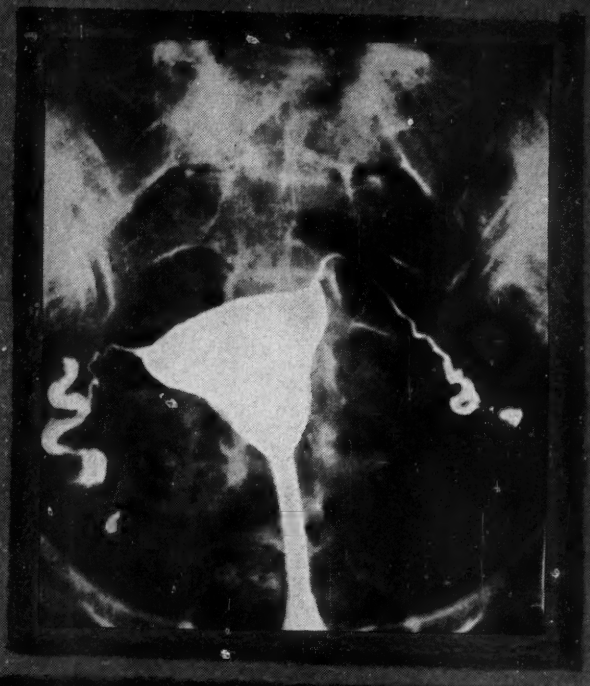
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*Page, E. W., and Page, E. P.: Obstet. & Gynec. *1*:94 (Jan.) 1953.

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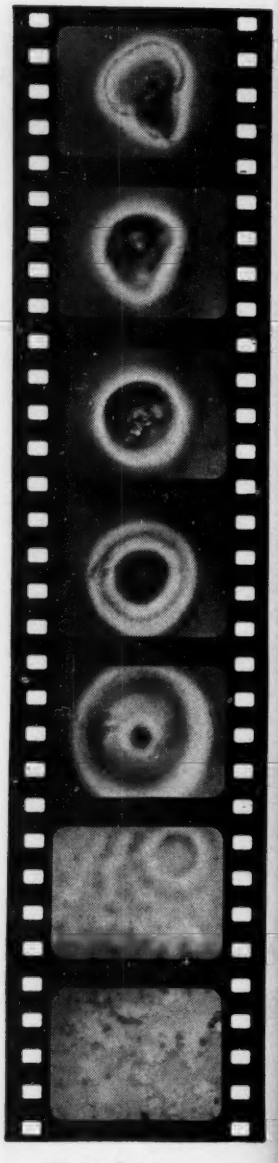
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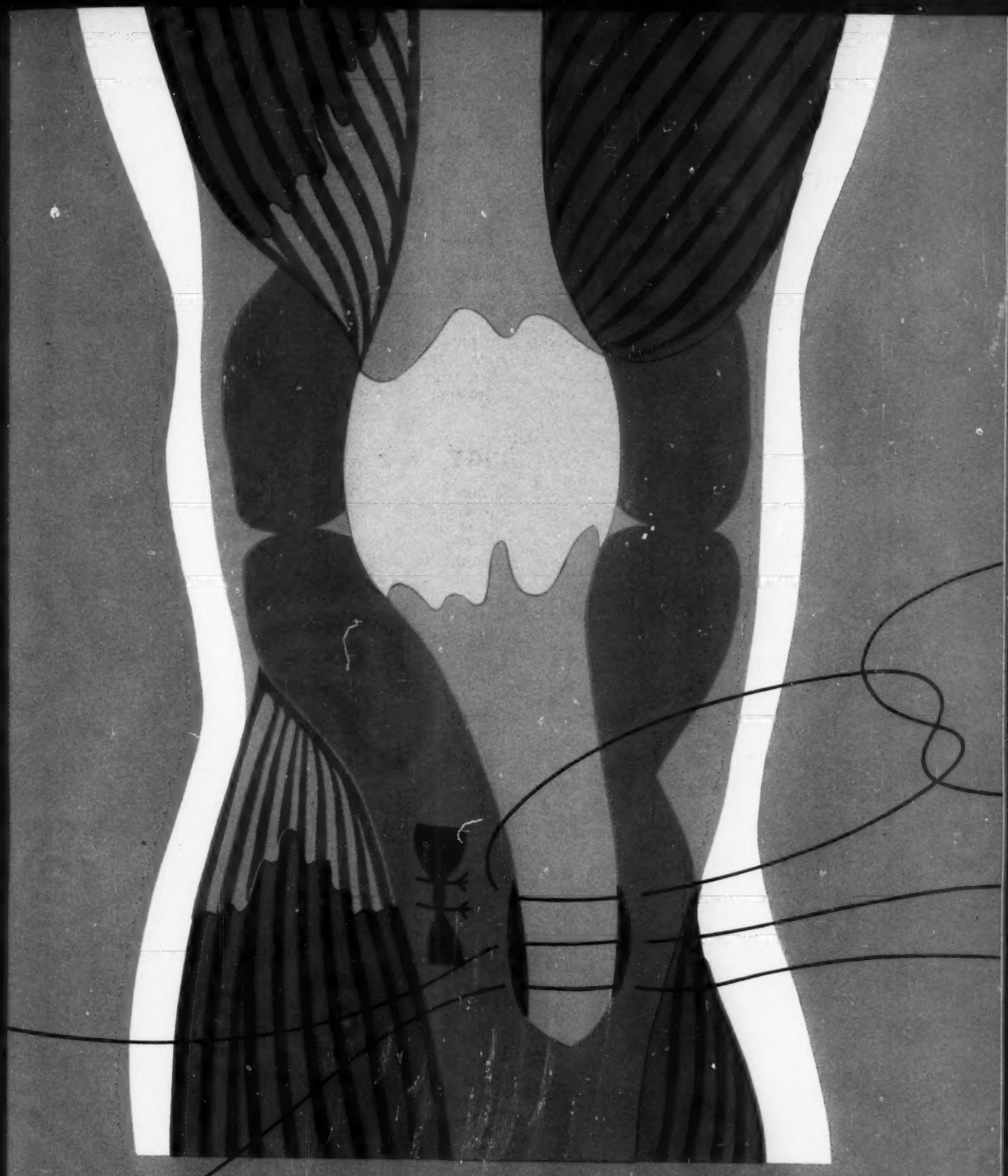
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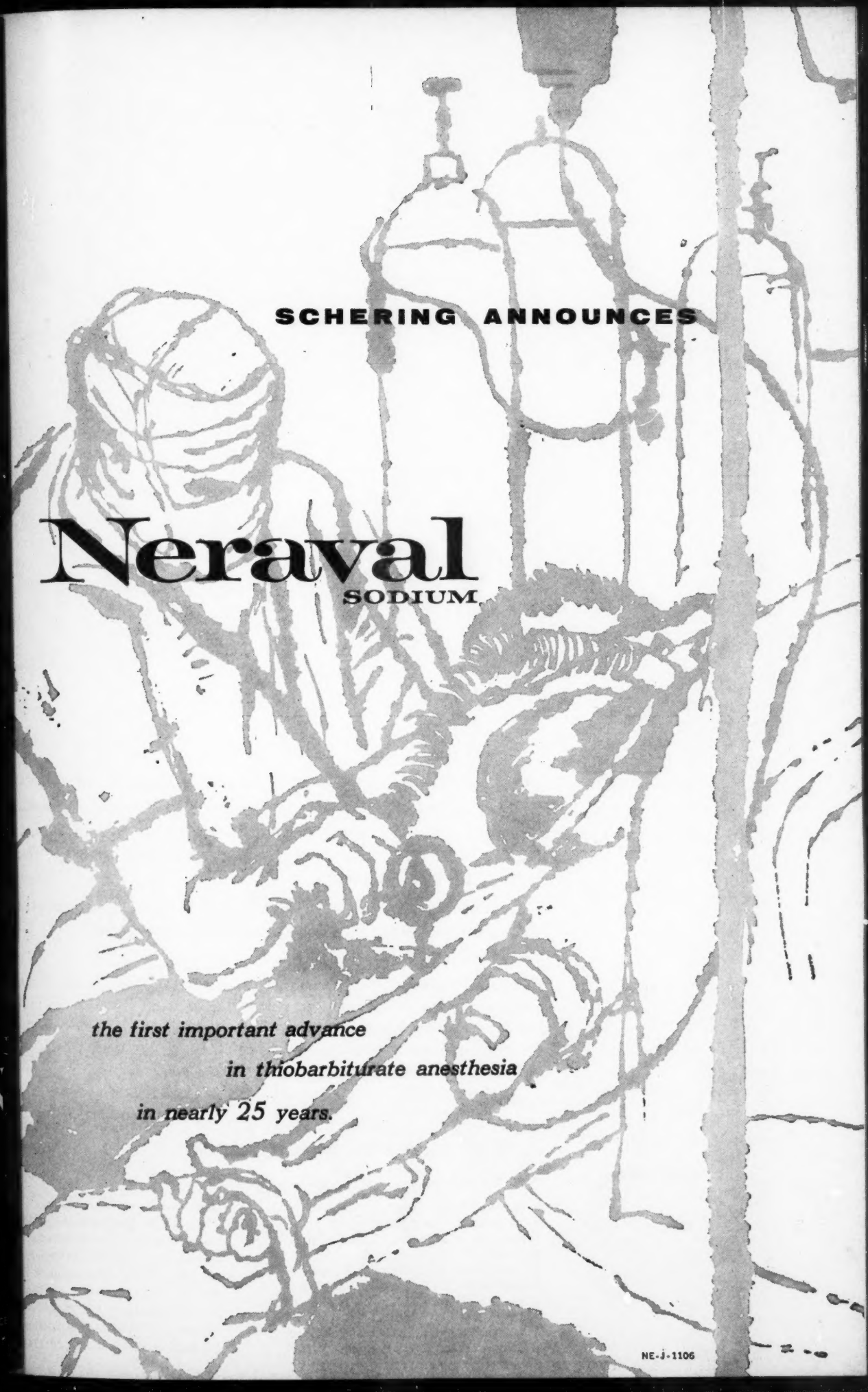
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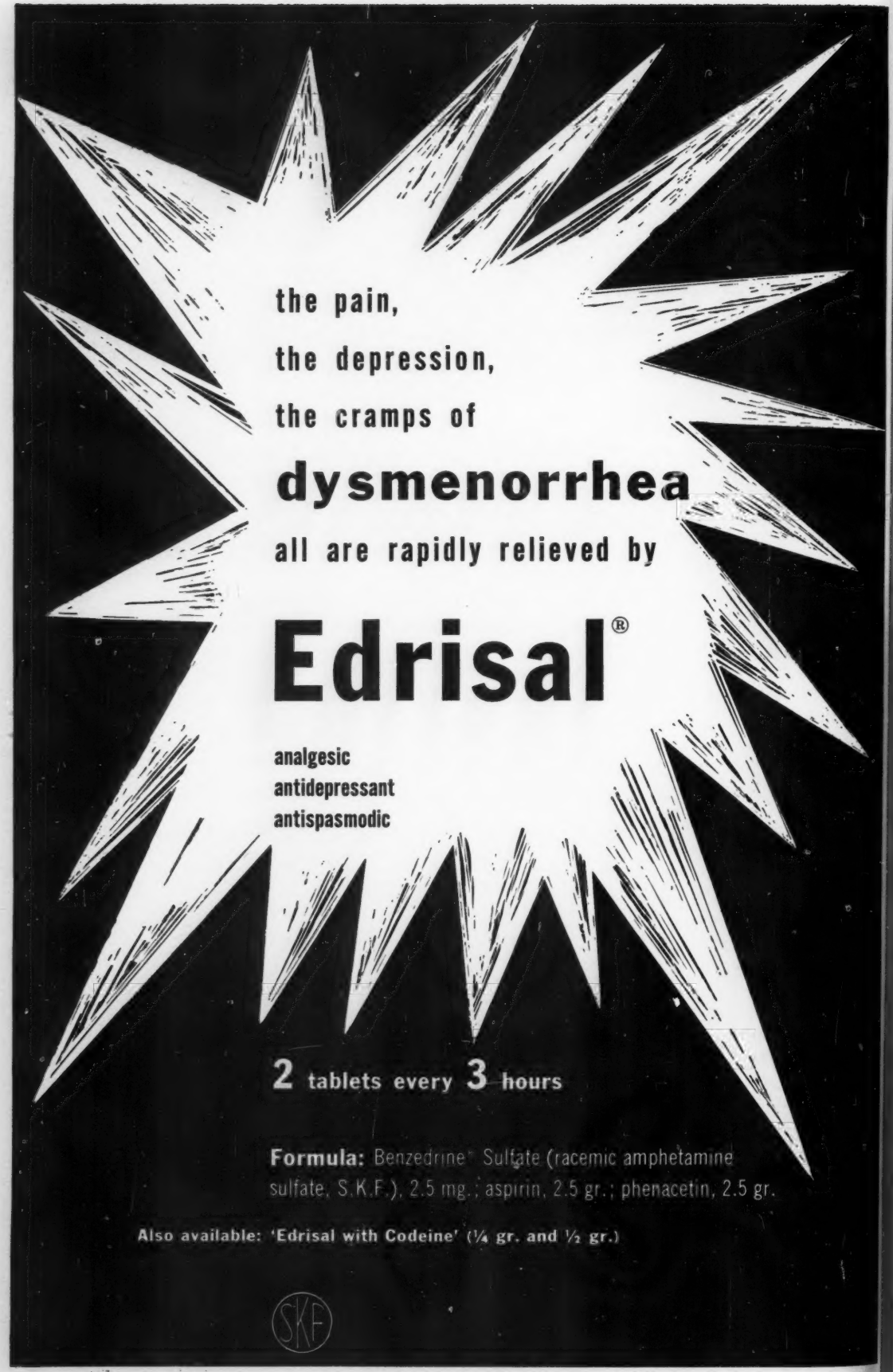
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MIGRAINE AND VASCULAR ALLERGY: Transactions of the Collegium Internationale Allergologicum, 2nd Symposium in Basel, 1955. Edited by R. R. A. Coombs, D. Harley and P. Kallos. 360 pp., 136 fig., 1956 (Separatum vol. 7, nos. 4-6, and vol. 8, nos. 1-2 "International Archives of Allergy and Applied Immunology") US $9.50

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Obstetrics

RENAL BIOPSIES FROM PATIENTS WITH "TOXEMIA OF PREGNANCY"*

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(From the Department of Obstetrics and Gynecology of the University of Chicago and the Chicago Lying-in Hospital)

MUCH work has been done during the past fifty years in an attempt to determine the etiology and sequelae of the so-called "toxemias of pregnancy" but there is still much confusion because of lack of agreement among investigators as to what symptoms and clinical findings warrant such a diagnosis. Edema, proteinuria, and hypertension, alone or in combination, have been variably used as criteria for the diagnosis of pre-eclampsia; but without proper definition none of these has significance.

Too often every pregnant woman with convulsions and/or coma has been classified as having eclampsia in spite of the fact that Dieckmann[6] has reported 19 diseases or conditions other than true eclampsia which have been associated with convulsions and/or coma in pregnancy or the early puerperium.

To distinguish a patient with true pre-eclampsia-eclampsia having its origin in an existing pregnancy from one who has had pre-existing hypertension on which the pregnancy is superimposed is often difficult and may be impossible if no data are available concerning the prepregnancy state. The criteria used for the differential diagnosis of pre-eclampsia and hypertensive toxemia are those described by Dieckmann.[6] The clinical diagnoses were made by W. D. and C. M.

*Supported in part by the 50th Anniversary Fund for Eclampsia and United States Public Health Service grant No. 3166 for medical research.

NOTE: The Editors accept no responsibility for the views and statements of authors as published in their "Original Communications."

The proteinuria, edema, and hypertension that make up the principal disturbances encountered in a toxemia of pregnancy point to the kidneys as a possible organ responsible for the disturbance. Renal function studies have been inconclusive in determining the specific nature of the renal change The rapidity with which function returns to normal after delivery indicates that whatever abnormality is present in pre-eclampsia-eclampsia is temporary and completely reversible.

Until very recently morphologic examination of the kidneys has been possible only on material obtained at autopsy. Most investigators have agreed that in patients who die of eclampsia a renal lesion is present but they have disagreed as to the nature of the lesion. One of the areas where there has been a complete lack of information in the study of toxemia is in knowledge concerning the structure of the kidneys during the acute phase of the disease. Studies of fatal cases give no information concerning the appearance of the kidney earlier in the course of the disease. It has long been realized that study of the kidneys during life would be extremely valuable. Such studies could determine whether the toxemia generally designated as pre-eclampsia was associated with a characteristic renal abnormality that would differentiate patients with pre-eclampsia from those who had had prepregnancy hypertension or other renal disease; and whether such an abnormality if present would show varying degrees of severity that could be correlated with clinical symptoms or could be used for prognosis. Whether any lesion that might be present is permanent or reversible could also be determined.

Ideally, kidney biopsies would be correlated with careful clinical and chemical studies both during the acute phase of the disease and after a lapse of six to twelve months.

It was in an attempt to answer these questions and to elucidate further the exact histology of the renal lesion in pre-eclampsia-eclampsia that the present study was undertaken.

Previous Studies Based on Autopsy Material

Löhlein[16] in 1918 is credited with being the first to recognize the glomeruli as the principal site of pathologic changes in eclampsia. He described swelling and increase in capillary endothelium and thickening of capillary walls and pointed out a resemblance to glomerulonephritis.

Fahr[9] in 1920 studied 28 cases of eclampsia and likewise found changes in glomeruli. The capillary walls were thickened, at times sufficiently to occlude the lumina and destroy endothelial cells. The tufts consequently generally showed a decreased rather than increased cellularity. The absence of leukocytes and the presence of fat droplets in the endothelium were considered evidence of a degenerative as opposed to an inflammatory origin and the condition was designated glomerulonephrosis. In later works (1928) he stated that the lesions may occur in pre-eclampsia as well as eclampsia and reiterated his belief that they were related to nephrosis and not to glomerulonephritis.

Bell[3] described the reduction in capillary lumina as the most striking change in the glomeruli and interpreted this as a result of thickening of the basement membrane and swelling of the epithelial cells surrounding the

capillaries. He thought that proliferation of endothelial cells or fibrillation of the basement membrane rarely occurred in eclampsia, these being the principal lesions of glomerulonephritis. The tubules were described as rarely abnormal except for the occasional presence of a few casts. He thought eclampsia and pre-eclampsia the same disease and in 51 cases subsequently described by him[4] as showing typical glomerular lesions, 20 had no record of convulsions. The abnormality of the glomerular lesions was considered mild in 3, moderate in 6, and severe in 11 of the kidneys from the 20 patients without convulsions.

Bell considered the normal glomerulus to be composed of capillary loops made up of a single basement membrane covered externally by epithelial cells and internally by endothelial cells without other "interstitial" or "mesangial" cells. This is the same pattern described more recently by Hall[11] as a result of his observations with the electron microscope.

Baird and Dunn[2] in 9 out of 10 cases of eclampsia described in glomeruli uniform changes consisting of enlargement, accentuated lobulation, and increased density of the tufts, with diminution or absence of erythrocytes. The capillary loops always appeared narrowed or closed because of thickening of the walls and an increase or enlargement of endothelial cells. Any seeming reduction in endothelial cells, described by Fahr, was attributed to swelling of cells without increase in nuclei. A striking feature was the uniform involvement of all glomeruli in any given case, although there was considerable difference between cases. They concluded the lesion was inflammatory and very similar to glomerulitis. They agreed with Bell that the two lesions could generally be distinguished but felt that the difference was one of degree rather than of kind.

They concluded that this renal lesion which appeared to diminish renal circulation was constantly present in eclampsia but that there was no relation between the severity of the convulsions and the degree of renal change and that this "eclamptic" lesion represented the "common nephritis of pregnancy which is usually mild in its effects and rarely threatens life." In a few women with convulsions they found histologic evidence of glomerulonephritis and interpreted this an indicating that glomerulonephritis might play the same role in the genesis of eclampsia as does the more frequent form of the glomerular lesion.

Canny[5] failed to find thickening of the basement membrane in eclampsia. He concluded that the changes in eclampsia are similar to, but less severe than, those in early glomerulonephritis. Both were described by him as showing avascularity of capillary loops and proliferation of endothelial cells. To him the absence of leukococytic infiltration differentiated eclampsia from glomerulonephritis.

McManus[17] also denied the thickening of the glomerular basement membrane. The characteristic lesion according to him is a fine reticulation and vacuolation of the intercapillary space with extension at times into adjacent endothelial capillary cells. This corresponds to edema of the tuft and can be made out best with the periodic acid-Schiff stain. He stated that with a hematoxylin-eosin stain the only change noticeable in the glomeruli "is a slight excess in cellularity, including the preservation of many visceral epithelial cells." Tubular changes consist of fat, colloid droplets, granular and hyaline casts, and other nonspecific lesions.

Sheehan[20] also thought there was no thickening of the basement membrane and attributed the abnormality of the glomeruli to changes in endothelial cells resulting in swelling and laying down of fine fibrils, either under the basement membrane or as a network between the cells. He thought these fibrils were

often erroneously misinterpreted as thickening and reduplication of the basement membrane. Epithelial cells over the loops were stated to become greatly thickened as a result of an increase in their cytoplasm. He is one of the few to describe an increase in caliber of any of the capillaries. He described the capillary loops as showing great variation in size with some ballooned out to twice their normal diameter and with others narrow and beaded. Tubular changes were stated to include flattening of the epithelium of the first convoluted tubules, the presence of occasional hyaline droplets in their cytoplasm, and partial obstruction of collecting tubules by casts of protein or hemoglobin derivatives.

Shehan thought the glomerular lesions were exaggerated in multiparas or elderly primiparas, possibly as a result of age or the severity of the vascular disturbance. Also, he stated that, in such patients occasional glomeruli show enlargement of a capillary loop to such an extent that it comes in contact with the capsule. This leads to local swelling of the basement membrane and development of endothelial fibrils in the form of a coarse hyaline network. The epithelium of the loop and the capsule proliferate at the site of the adhesion to form a small crescent.

Allen[1] supported Bell's description of thickening of the basement membrane and ischemia of the glomeruli and stated it was sufficiently characteristic to establish the diagnosis of toxemia of pregnancy. He also stated that endothelial cells may or may not be increased and swollen and that occasionally focal fibrinoid, eosinophilic alteration of glomerular basement membranes simulates the glomerular "wire-loop" change of disseminated lupus erythematosus. The tubules are not seriously altered although they may show hydropic, fatty, or hyaline degeneration and infrequently focal necrosis.

Allen designated the lesion found in toxemia of pregnancy as acute membranous glomerulonephritis and related it clinically and histologically to the chronic membranous glomerulonephritis found in lipoid nephrosis. He reported that in the acute form (pregnancy toxemia) the renal lesions disappear if the patient survives pregnancy while the chronic form (lipoid nephrosis) is invariably fatal.

Jones[13] stated that "in eclampsia the edema in the swollen glomeruli produces a beautiful separation of the endothelial and epithelial basement membranes," and used this to support his contention that two basement membranes with intervening interstitial cells are present in the normal glomerulus. He stated further that "in acute glomerulonephritis in its earliest stages one may find examples of edema of the glomerulus which approach those seen in eclampsia." In 1953 he[14] commented that "in acute glomerulonephritis there is tremendous edema and inflammation in the connective tissue space between epithelium and capillary endothelium, while in lipoid nephrosis and eclampsia the change in this connective tissue is extremely mild."

In relation to toxemias of pregnancy Rinehart and associates[19] stated, "The glomerular lesions of eclampsia bear some resemblance to the so-called membranous glomerulonephritis encountered in the nephrotic syndrome. The endothelial element of the eclamptic glomerulus appears thickened and may show some longitudinal fibrillation. Most glomeruli are essentially devoid of blood." They observed several patients with eclampsia who also had lower nephron nephrosis with partial disruption of the distal convoluted tubules and formation of granular hemoglobin-containing casts.

Govan[10] studied 33 cases of fatal eclampsia and described local proliferation of endothelial cells, increase in mesangium due to expansion of the intercapillary space, and irregular swelling of the mesangial aspect of the capillary basement membrane as the most outstanding changes. Hyaline droplets were

found in the mesangium and glomerular epithelium, and also in the epithelium of the first convoluted tubules. Subendothelial hyaline deposits were present in the afferent arterioles and some of the cortical arteries. He said the epithelial cells of the glomeruli were more prominent because of swelling, but were not increased in number. The fibrillary character of the mesangium he found particularly well shown by the periodic acid-Schiff stain. The occlusion of the capillaries was described as due to endothelial cell proliferation.

He suggested that mesangial changes are characteristic of pregnancy per se and that the increase found in toxemia is a result of exaggeration of this altered state. A number of references from the literature were cited to the effect that toxemia is more common with altered endocrine states and he thought that a disturbance in hormone balance might be responsible for the glomerular lesions.

Hall's[11] recent investigations of the glomerulus with the electron microscope are of interest in relation to the descriptions of changes in interstitial cells and mesangium, and the separation of two basement membranes. He has given a very convincing description of the glomerulus as composed only of endothelial and epithelial cells with an intervening basement membrane. He has found no evidence of interstitial cells and has concluded they do not exist. Consequently, the framework of interstitial connective tissue called mesangium by which capillaries are often stated to be supported within the glomerulus must also be nonexistent.

If this is the true structure of the glomerulus, and it seems most reasonable to us that it is, changes associated with eclampsia cannot be edema and separation of two basement membranes, increase in interstitial cells or mesangium, or fibrillation of interstitial cells. The changes can result only from alteration in the basement membrane or endothelial cells, since epithelial cells are not involved in the process.

Studies on Living Patients

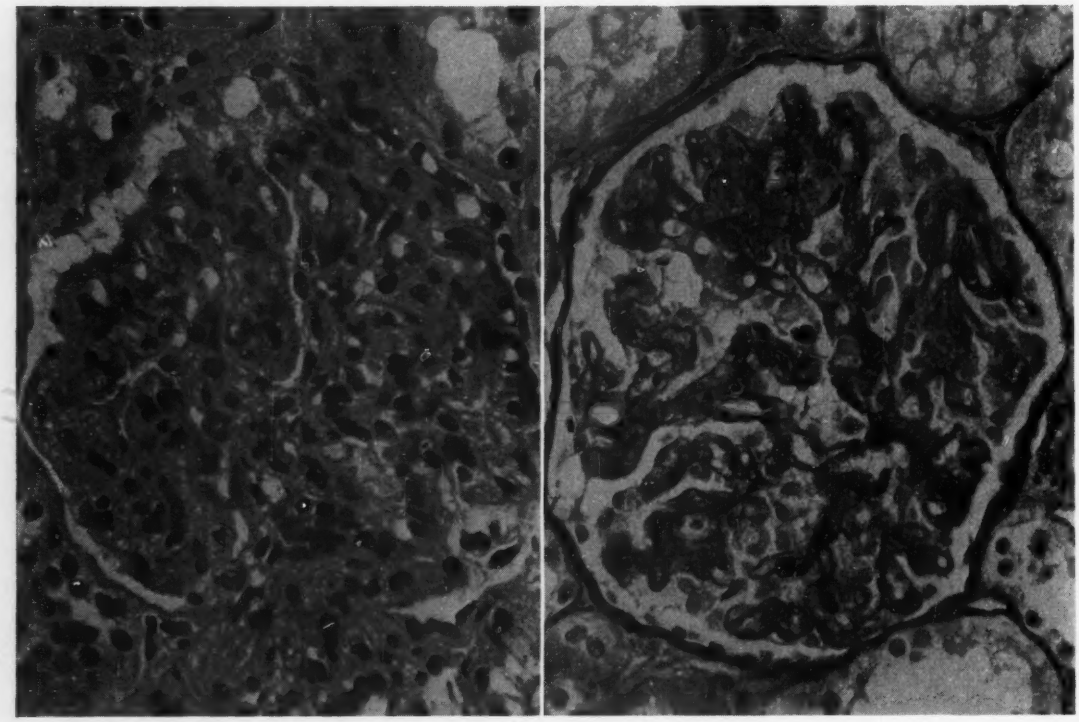
The first percutaneous renal biopsies were reported in 1951 by Iversen and Brun[12] who were able to obtain satisfactory material in about 50 per cent of their attempts. Kark and Muehrcke[15] in 1954 reported over 200 biopsies and stated that over 80 per cent of all the biopsies they had attempted were successful in showing 5 or more glomeruli. In 1954 Siegler and Malfetano[21] reported two percutaneous biopsies in postpartum patients but Dieckmann's report[8] in 1954 seems to have been the first concerned with biopsies obtained during pregnancy. Since then Pollak and associates[18] stated that in 4 patients who were studied by repeat biopsy two to seven months after pre-eclampsia the glomerular lesion had disappeared. In some patients with toxemia the glomerular lesion is not reversible.

Present Investigation

Our first renal biopsies were obtained by the transperitoneal route in 1948; we subsequently changed to the percutaneous route using the Iversen and Brun needle and technique and finally to a modification of the method outlined by Kark and Muehrcke,[15] using the Franklin modification of the Vim-Silverman needle. We no longer obtain a pyelogram, as earlier investigators advised, but rely on the anatomic position of the kidney and movement with respiration of the exploring needle. If we cannot locate the kidney, we obtain a pyelogram.

We have continued, where possible, to obtain biopsies at the time of cesarean section or at tubal ligation. This has required a right rectus incision, which at times has been extended 2 to 3 cm. above the umbilicus. In most instances the

right kidney has been sufficiently mobile so that it could be brought into the field in the event that serious bleeding occurred. In general the peritoneum has been incised and reflected, the capsule of the kidney cut, and a Van Doren cervical punch used to obtain the biopsy. In a few instances the biopsy was obtained with a knife. Gelfoam and thrombin were always available, but in almost every instance a mattress suture controlled the bleeding. In a few cases the cecum and ascending colon were reflected as if one were going to ligate the inferior vena cava; this gave excellent exposure. In a few instances the left kidney, which is usually the higher, was more easily reached than the right. If the kidney was fixed high and close to the diaphragm, the aspiration needle was used to obtain the biopsy through the opened abdomen. We have compared biopsies from upper and lower poles and from both kidneys and have concluded that if a pathologic condition is present, a single adequate



A. *B.*

Fig. 1.—*A*, V. T., Case 21. Glomerulus from primiparous patient with clinical diagnosis of hypertensive toxemia showing changes similar to those observed in pre-eclampsia. Hematoxylin-eosin stain showing reduction in capillary lumina associated with a seeming increase in cytoplasm. (×690; reduced ⅓.)

B. V. T., Case 21. PAS stain showing thickening and fibrillation of basement membrane and an increase in epithelial cells. (×595; reduced ⅓.)

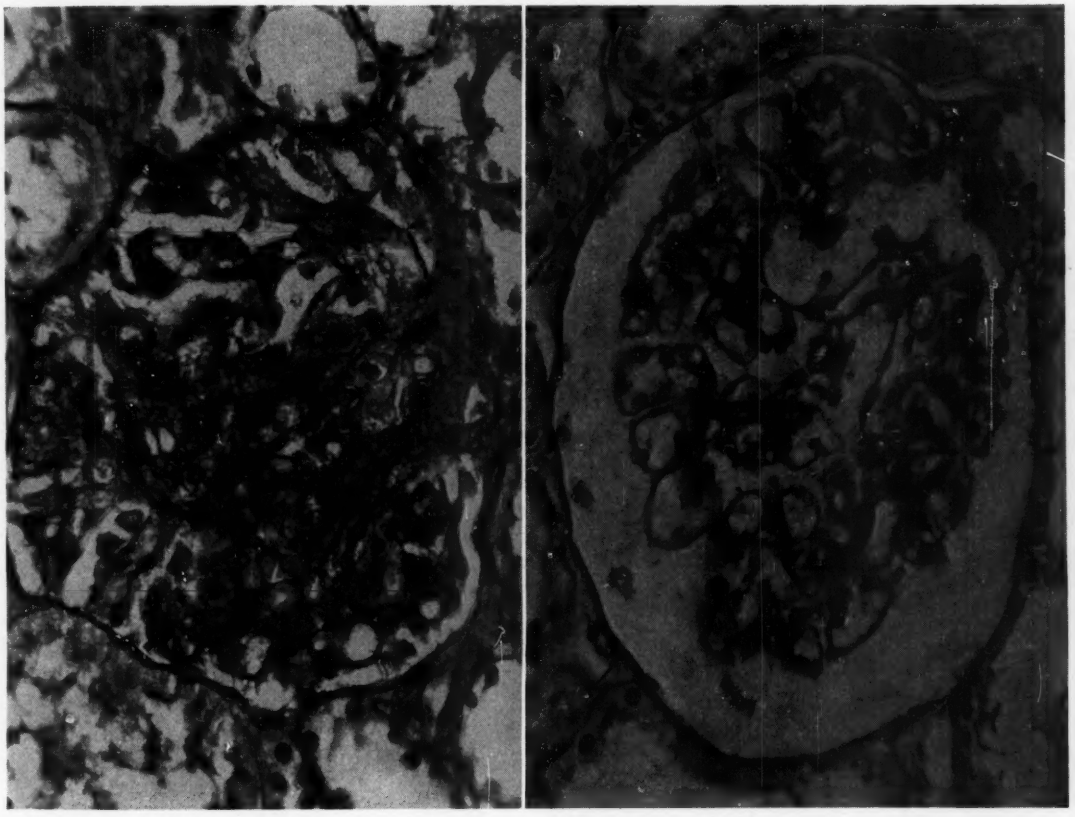
biopsy will reveal it. Two biopsies not obtained within one hour after delivery were obtained sometime during the first seven days of the puerperium. Like all procedures, renal biopsy is not without danger, but in our entire series no patient has died and only one required transfusions.

Between 1948 and Dec. 1, 1955, we have obtained satisfactory renal biopsies in 122 living pregnant or recently pregnant patients. Sixty-nine were transperitoneal and 53 were percutaneous (by C. M.). The former comprise 96 per cent of the cases in which an attempt to obtain a biopsy was made and the latter comprise 68 per cent (an increase from 40 to 75 per cent). These include patients with diagnoses of different kinds of renal pathologic conditions; among

them also were 19 patients with a normal pregnancy 5 of whom had had pre-eclampsia in a previous pregnancy. The present report includes the first 71 patients on whom satisfactory renal biopsies were obtained.

All material was fixed in 10 per cent neutralized formalin and was prepared with hematoxylin-eosin and PAS stains. Multiple sections from each biopsy were examined.

From examination of our material (by E. P.) it seems probable that all investigators have been seeing the same lesions and that the reasons for disagreement have been (1) the inclusion of patients with pre-existing kidney disease in some series and (2) the inability to determine conclusively by any histologic means what is actually responsible for the reduction in glomerular capillary space. Each investigator has looked at the same lesion; some have



A. *B.*

Fig. 2.—*A*, P. C., Case 9. Glomerulus from kidney biopsy taken at height of signs of severe pre-eclampsia. The basement membrane is irregularly thickened but in many places cannot be identified because of diffuse fibrillation. The capillary lumina are decreased in caliber and many appear to be completely occluded. This is typical of the severe involvement indicated as 3+. (PAS stain. ×680; reduced ⅓.)

B, P. C., Case 9. Glomerulus from kidney biopsy taken two years after original biopsy. No abnormalities are visible at this time. (PAS stain. ×550; reduced ⅓.)

thought that the endothelial cells, some the interstitial cells, and some the epithelial cells were increased. Some have thought there was (1) a thickening of a single basement membrane; (2) an edematous separation of two basement membranes; (3) fibrillation of a basement membrane, and others have thought the fibers were laid down in (4) endothelial, (5) interstitial, or (6) epithelial cells, or (7) that the apparent fibrillation was only a reticulation of cytoplasm.

In our own material we have found cases that could be used to illustrate almost any of these points. The typical lesion usually described as characteristic of eclampsia (and also present in pre-eclampsia, as we will show) is in the glomeruli. It is fairly diffuse although there may be some variation in the severity of involvement in adjacent glomeruli. With a hematoxylin-eosin stain the glomeruli appear unusually solid with a considerable reduction in caliber of capillary lumina (Fig. 1, *A*). The cytoplasm seems increased in amount. Epithelial cells covering the outer surface of the glomerular tufts are often unusually large and prominent and at times are free in Bowman's space. The nuclei of the endothelial cells are not appreciably increased in number.

With a PAS stain considerably more detail can be made out. A diffuse, finely fibrillar material that can be variously described as fibrillation of basement membrane or reticulation of cytoplasm can be identified as the apparent cause of the reduction in capillary lumina (Fig. 1, *B*). Sometimes the basement membrane is solidly thickened and sharply demarcated but at other times it merges with and cannot be definitely delineated from adjacent extremely fine fibrils. The process of fibrillation does not seem to involve epithelial cells but otherwise it cannot be definitely located. However, if Hall's interpretation of his electron microscope studies are correct and interstitial cells and mesangial tissue are not present, the alteration must be a result of splitting of the basement membrane and/or elaboration of fibrils by endothelial cells. On the other hand, what appear to be fibrils may be only local condensation of cytoplasm, a condition which McManus has described as reticulation. Changes in tubules are inconspicuous or nonspecific and arterioles show no intimal proliferation or hyalinization. In a few cases scattered, completely hyalinized glomeruli are visible. They are probably due to some previous disturbance, which has resulted in healing of the majority of glomeruli with complete destruction of a few. There is no reason to believe they are specifically related to the lesion under discussion.

In the present study we have attempted to divide the kidneys, showing the changes in glomeruli thought to be related to pregnancy into three groups. The group designated as severe (3+) includes all those showing marked reduction in capillary lumina associated with thickening of basement membrane and large amounts of fibrillar material in the cytoplasm (Fig. 2, *A*). The second group designated as moderate (2+) includes those with similar changes but with slightly less reduction in capillary lumina. The third group designated as mild (1+) is composed of those in which the basement membrane is only slightly thickened and only a few fibrils are present in cytoplasm. The glomerular pattern is much less disturbed but cannot be considered normal. Some observers might interpret part of the kidneys in this last group as within the limits of normal. Since we believe there are abnormalities, however, it seems wise to record them even though they are mild. The appearance suggests that they are incipient changes which, under provocation, might progress to produce a more pronounced disturbance.

The differences demonstrable with a hematoxylin-eosin stain and with a periodic acid-Schiff stain are shown in Fig. 1, *A* and *B*. Fig. 1, *A* shows only reduction in capillary lumina and a diffuse increase in cytoplasm. Fig. 1, *B* shows the apparent increase in cytoplasm to be due to increase in thickness of basement membrane and fibrils in cytoplasm, as well as a marked increase in the size and number of epithelial cells.

Renal Biopsies

The 71 patients from whom our renal biopsies were obtained include 26 primiparas and 45 multiparas; 2 patients are included in both series.

Table I shows pertinent data for 26 primiparas, 19 of whom were also primigravidas. The 7 who were not primigravidas had had one or more abortions before the twentieth week. The clinical diagnoses in these cases were eclampsia 3, pre-eclampsia 11, hypertensive disease 7, glomerulonephritis 4, normal pregnancy with postpartum hypertension 1. The diagnoses were made during pregnancy or before discharge from the hospital and were not changed by the appearance of the renal biopsy, the examination at 4 to 6 months post partum, or by the course in another pregnancy. The diagnoses of hypertensive disease or chronic glomerulonephritis were not all confirmed by the renal biopsies. However, a longer follow-up may show the clinical diagnosis to have been correct.

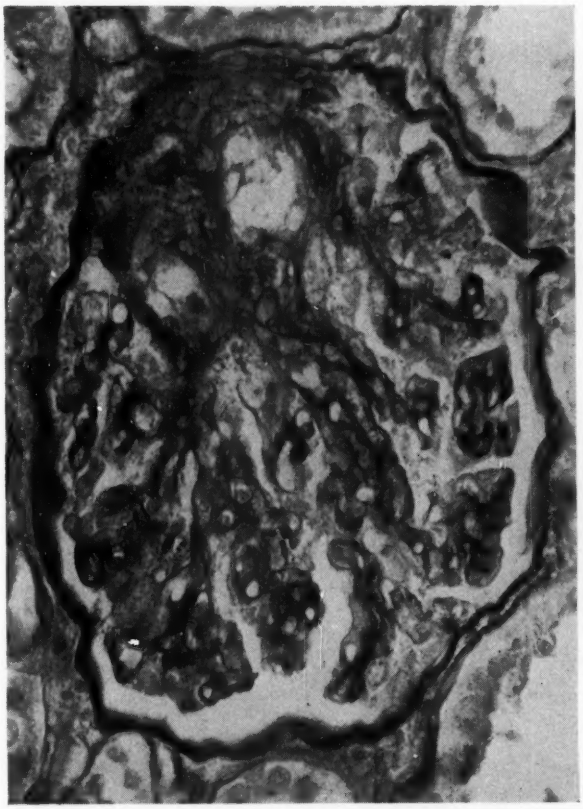


Fig. 3.—E. N., Case 13. Glomerulus from kidney biopsy of patient with possibly mild pre-eclampsia. The lumina of the capillaries are greatly decreased in caliber. The basement membrane is moderately thickened and markedly fibrillated. (PAS stain. ×700; reduced ⅓.)

The diagnoses on renal biopsies were made without knowledge of the clinical condition.

Among the 26 primiparas there were 22 who were thought to have some change in the glomeruli characteristic of the lesion under discussion; of these 9 had the typical, full-blown change described as 3+, 9 had 2+, and 4 had 1+. Four patients had no glomerular lesions; in 2 the kidneys were considered normal and in 2 the arterioles appeared sclerotic (Table II). The 18 with 2+ or 3+ glomerular lesions include 2 patients with eclampsia, 11 with pre-eclampsia, and 5 with a clinical diagnosis of hypertensive disease.

TABLE I. PRIMIGRAVIDAS, CLINICAL FINDINGS AND KIDNEY CHANGES

NO.	AGE (YEARS)	GRAVIDITY	EDEMA	AVERAGE MAXIMUM BLOOD PRESSURE (MM. HG.)	PROTEINURIA (GM./24 HOURS)	FUNDUSCOPIC* CHANGES	WEIGHT OF BABY (GRAMS)	ADDIS COUNT† CHANGES	CLINICAL DIAGNOSIS	KIDNEY GLOMERULAR CHANGE
1. M. He.	32	ii	2+	190/110	10.0	Slight	(a) 780 (b)	Marked	Eclampsia	+
2. M. Hi.	22	i	—	220/140	4+		(a) 4,185	Moderate	Eclampsia	++
3. M. Ha.	35	i	4+	230/130	12.0	Slight	(a) 710 (b)	Marked	Eclampsia	+++
4. L. W.	18	i	2+	180/125	5.0	Normal	1,120	Marked	Pre-eclampsia (f)	+++
5. R. I.	18	i	4+	170/110	5.38	Moderate	1,870	Moderate	Pre-eclampsia	++
6. C. A.	14	i	2+	150/104	6.0	Normal	2,395	Marked	Pre-eclampsia	++
7. H. S.	13	i	2+	160/110	2.1	Normal	2,790	Normal	Pre-eclampsia	++
8. D. B.	22	i	+	160/100	+	Normal	2,875	0	Pre-eclampsia	++
9. P. C.	20	i	4+	190/100	6.0	Slight	(a) 1,183	Moderate	Pre-eclampsia	+++
10. B. K.	26	i	3+	170/120	0+	Normal	1,515	Slight	Pre-eclampsia	+++
11. M. S.	20	i	2+	170/115	0.1	Slight	1,825	Marked	Pre-eclampsia	+++
12. E. L.	23	ii	4+	180/100	6.1	Slight	(a) 2,750	Slight	Pre-eclampsia	+++ (d)
13. E. N.	23	i	1+	135/85	9.0	Normal	3,515	Marked	Pre-eclampsia	+++
14. Q. W.	31	iii	2+	150/100	2.0	Normal	3,710	Marked	Pre-eclampsia	+++
15. A. S.	42	ii	2+	205/110	11.0	Normal	(a) 645 (b)	Marked	Hypertensive disease	++
16. D. W.	33	iv	0	210/135	8.2	Slight	860 (c)	Marked	Hypertensive disease	none (e)
17. R. B.	36	i	0	230/135	1.9	Marked	1,465	Moderate	Hypertensive disease (f)	++
18. A. M.	38	i	1+	150/100	1.0	Slight	3.050	Normal	Hypertensive disease	++

19. L. B.	37	i	1+	160/110	6.4	Normal	(a)	3,135	Marked	Hypertensive disease (f)	++
20. E. S.	42	ii	0	240/125	0.2	Moderate	(a)	1,710	Marked	Hypertensive disease (g)	none (e)
21. V. T.	24	i	0	160/110	8.0	Marked	(a)	2,895	Slight	Hypertension	+++
22. M. C.	34	i	1+	130/80 200/140 Post partum	0.3	Normal		3,305	Normal	Postpartum hypertension	none
23. R. F.	25	i	0	130/75	+	Normal		0	Moderate	Chronic glomerulonephritis (g)	none
24. L. R.	32	i	±	150/80	0.2	Moderate	(a)	93 (abortion)	Marked	Chronic glomerulonephritis	+
25. A. K.	40	i	1+	190/110	10.0	Normal		367 (abortion)	Marked	Chronic glomerulonephritis (g)	+
26. J. J.	23	ii	0	130/90	2.0	Normal		3,410	Moderate	Chronic glomerulonephritis (g)	+

*Codes for ophthalmoscopic examination:
Slight, Grade I hypertensive retinopathy or mild local arteriospasm.
Moderate, extreme attenuation of arterioles, Grade II hypertensive retinopathy.
Marked, Grade III; hemorrhages, exudates, etc.

†Code for Addis count:

	CASTS	ERYTHROCYTES (MILLIONS)	LEUKOCYTES AND EPITHELIAL CELLS (MILLIONS)	PROTEIN (GM./24 HOURS)
Normal	5,000	0.4	0.03–1.0	0.03
Normal pregnancy changes	10,000	0.5–0.9	0.03–1.0	0.04 0.2 voided urine
Slight, I	20,000–50,000	0.5–0.90	1.0	0.2–0.9 +
Moderate, II	100,000–900,000	1–40	1.0–4.9	1–2.9 ++ +++
Marked, III	1.0 M.+	50 +	5.0	3.0 + ++++

(a) Operative termination of pregnancy by hysterotomy or cesarean section.
(b) Born living but died.
(c) Stillborn.
(d) Kidney showed old scars.
(e) Kidney showed sclerotic arteries.
(f) Prepregnancy hypertension.
(g) Prepregnancy proteinuria.

The 11 patients with a clinical diagnosis of pre-eclampsia all showed a moderate or severe (2+ or 3+) change in the glomeruli. Two of the 3 eclamptic patients showed a similar severity of the lesion while in one it appeared considerably more mild. There seems little doubt from these cases that the glomerular abnormality long considered characteristic of eclampsia is also found in pre-eclampsia and of a degree as great as in eclampsia. In fact, the severity of the clinical symptoms cannot be judged by the disturbance in the glomeruli for in several instances the most marked histologic changes were associated with relatively mild clinical symptoms, and one case of eclampsia showed only mild histologic abnormality (Fig. 3). That there is a glomerular lesion associated with pre-eclampsia, however, cannot be doubted.

The group of patients with the diagnosis of hypertensive disease is extremely interesting. Of the 7 only 2 showed arteriosclerosis and these had normal glomeruli, while the other 5 showed moderate or severe glomerular lesions of the variety described above. The clinical diagnosis in the 2 with sclerotic vessels and one other was made on the basis of knowledge of an elevated blood pressure prior to pregnancy and the diagnosis of hypertensive disease was made in the others on symptoms occurring during pregnancy. Of particular note is the fact that only one of the 5 was less than 36 years of age. These patients with a clinical diagnosis of hypertensive diseases are the oldest patients in the group of primiparas. The average age of all those with a clinical diagnosis of hypertensive disease was 36 years, of those with a diagnosis of pre-eclampsia was 20.7 years.

TABLE II. KIDNEY LESIONS IN PRIMIPARAS

	PATHOLOGIC DIAGNOSES					
		GLOMERULAR LESIONS				
CLINICAL DIAGNOSIS	NORMAL	1+	2+	3+	ARTERIOLO-SCLEROSIS	TOTAL
Eclampsia		1	1	1		3
Pre-eclampsia			4	7		11
Hypertensive disease			4	1	2	7
Chronic glomerulonephritis	1	3				4
Normal	1					1
Total	2	4	9	9	2	26

These patients with hypertensive disease, in spite of being primiparas, had a clinical picture not entirely characteristic of pre-eclampsia. All were older than the usual pre-eclamptic patient, one was reported to have marked changes in retinal vessels, although 2 had normal eye grounds and one showed only a slight change. One additional patient (No. 24) had a diagnosis of probable glomerulonephritis made during pregnancy (which terminated in an abortion) on the basis of moderate funduscopic changes a markedly abnormal Addis count, and slight elevation in blood pressure. Thus, of 21 primiparous patients who had definite glomerular changes, only 3 were known to have had previous hypertension.

Three interpretations of the renal lesions in the women with clinical diagnoses of hypertensive disease are possible: that the clinical diagnosis was in error and these patients were truly suffering from pre-eclampsia; that they had hypertensive disease with superimposed renal changes characteristic of pre-eclampsia; or that the glomerular change is not peculiar to pre-eclampsia but may be found in any pregnant woman with hypertension and proteinuria.

The 4 primiparous patients who were described as having only 1+ changes included 3 (Nos. 24, 25, 26) who were considered to have glomerulonephritis, and one (No. 1) with eclampsia. In 2 patients the clinical diagnosis of glomeru-

lonephritis was based largely on the knowledge that there had been proteinuria prior to pregnancy, associated in one with a high Addis count and very severe proteinuria during pregnancy. It is surprising that one of the patients with eclampsia had only a 1+ glomerular change.

The 2 primiparous patients who showed no glomerular changes of the variety under discussion included one (No. 22) who was normal until the postpartum period when hypertension developed and one (No. 23) with a diagnosis of glomerulonephritis based on the known presence of proteinuria before pregnancy although there was no abnormality during pregnancy except proteinuria.

The lesions in the kidneys of the multiparous patients are somewhat harder to evaluate than those in the primiparous. Dieckmann believes that pre-eclampsia does not ordinarily occur in women who have had a preceding pregnancy that has reached the period of viability unless some condition such as twins or polyhydramnios is present.

Among the 45 multiparous patients the clinical diagnoses were: hypertensive disease 26, chronic glomerulonephritis 5, normal pregnancy 12 (6 of whom had a history of toxemia in a previous pregnancy) diabetes mellitus 1, and not pregnant 1. The patient who was not pregnant, the one with diabetes, and 8 of the 12 with normal pregnancies showed normal kidneys. The remaining 4 with normal pregnancies were thought to have a mild (1+) pre-eclamptic change. The 5 patients with a clinical diagnosis of glomerulonephritis had the diagnosis confirmed in 3 instances while one kidney was normal and one was interpreted as having a moderate pre-eclamptic glomerular change and an occasional completely hyalinized glomerulus (Table III).

Of 26 in whom a clinical diagnosis of hypertensive disease was made, only 3 showed histologic evidence of existing renal pathology that could be considered as antedating pregnancy. These included one patient with arteriosclerosis (Case 7) who also had a biopsy a year later which showed increased abnormality, one with glomerulonephritis, and one with pyelonephritis. Five additional patients had one or more hyalinized glomeruli in each microscopic section but no evidence of sclerosis of vessels or chronic abnormality in remaining glomeruli.

TABLE III. KIDNEY LESIONS IN MULTIPARAS

	PATHOLOGIC DIAGNOSIS									
		GLOMERULAR LESIONS					ARTE-RIOLO-SCLE-ROSIS	CHRONIC GLOMER-ULONE-PHRITIS	PYE-LONE-PHRI-TIS	
		1+		2+		3+				
CLINICAL DIAGNOSIS	NOR-MAL	NO SCAR	WITH SCAR	NO SCAR	WITH SCAR					TOTAL
Hypertensive disease	4	10	3	3	2	1	1	1	1	26
Glomerulonephritis	1				1			3		5
Normal, no history of toxemia	3	3								6
Normal with history of toxemia	5	1								6
Not pregnant	1									1
Diabetes mellitus	1									1
Total	15	14	3	3	3	1	1	4	1	45

The fact that the remaining patients with diagnoses of hypertensive disease had no histologic changes on which a diagnosis of hypertension could be based by no means excludes the possibility that the patients were suffering from clinical hypertensive disease. In the early stages of essential hypertension sclerosis of renal vessels is almost never present, and even when the hypertension has been long standing pathologic changes may not be demonstrable.

Among the 23 patients without a diagnosis of pre-existing renal disease there were 5 who showed a moderate (2+) and 1 a severe (3+) glomerular lesion of the pre-eclamptic variety. Two of those with moderate changes also had a few completely hyalinized glomeruli. Of the remaining 17 patients, 4 had biopsies in which the renal tissue was considered normal and 13 had biopsies interpreted as showing a mild (1+) pre-eclamptic change.

We have been anxious to know whether the microscopically demonstrated glomerular lesions in pre-eclampsia persist to be the cause of permanent kidney damage or whether they disappear more or less simultaneously with cessation of clinical symptoms. We have obtained biopsies in subsequent normal pregnancies from 5 women with pre-eclampsia in a preceding pregnancy; in all instances the biopsies during the normal pregnancy revealed normal glomeruli. One patient who is included in our group of primiparas because of severe pre-eclampsia in her first pregnancy (Case 9, Fig. 2, *A*) is also included with the multiparas as showing normal glomeruli in a normal pregnancy 2 years later (Fig. 2, *B*). In all our material there is no evidence that the glomerular change characteristically present in pre-eclampsia persists or is responsible for any permanent kidney damage.

Comment

It had been hoped in beginning this study on the histologic structure of the kidneys in patients with hypertension, proteinuria, and edema during pregnancy that it might be possible to differentiate pre-eclamptic from hypertensive toxemia by this means, since this is often difficult to do on the clinical information that can be obtained during the course of a single pregnancy. The data have been somewhat disappointing in this regard but they have nevertheless given information of considerable value.

There is no doubt but that a lesion exists in the glomeruli of some pregnant women which has a characteristic pattern unlike that found in any other condition. This is the picture described earlier in this paper as moderate (2+) or severe (3+) glomerular change. It was found in all of 11 primiparas with a clinical diagnosis of pre-eclampsia and in 2 of 3 with eclampsia, but it was also present in 5 of 7 primiparas with a diagnosis of hypertensive disease, as well as in 6 of 26 multiparas with a diagnosis of hypertensive disease.

We have designated as showing a mild (1+) change a group of patients who appear to have only a little thickening of basement membrane and slight fibrillation with no appreciable reduction in capillary lumina. Although there seems no doubt that there would be almost universal agreement among different investigators concerning the diagnosis of the more advanced changes, it is possible that in this group there would be considerably more difference of opinion. The diagnosis of 1+ involvement was made in 4 primiparas, 1 with a clinical diagnosis of eclampsia and 3 with glomerulonephritis. It was made in 17 multiparas, 13 with a diagnosis of hypertensive disease and 4 with normal pregnancies. We have not observed this condition in biopsies taken from nonpregnant women although our series (not reported here) is too small to be certain that it may not occur. The relatively frequent occurrence in women with a diagnosis of hypertensive toxemia suggests that this may be an early stage of the patchy fibrillation that has been reported in some cases of

hypertensive disease, or it may be a nonspecific change associated with any condition placing unusual stress on the kidneys. These data seem to necessitate the conclusion that only the change designated as moderate or severe should be considered characteristic of a "toxemic" lesion. What form of toxemia this lession indicates still remains to be answered. Its occurrence in all our cases of pre-eclampsia shows that it is extremely common in this condition, and might be considered as constant in pre-eclampsia-eclampsia were it not for the one case of eclampsia where only a 1+ change was observed. The presence of the lesion in 11 additional patients with a diagnosis of hypertensive toxemia (5 primiparas and 6 multiparas) and 1 with a diagnosis of glomerulonephritis is the complicating factor. This can be explained only as a result of one of three things: the lesion is not specific for eclampsia-pre-eclampsia as has been previously thought, but may occur also in pregnant patients with hypertensive disease; the division of these patients into the two groups, pre-eclampsia and hypertensive disease, is not justified and all should be considered as suffering from the same fundamental disturbance; pre-eclampsia may become superimposed on a pre-existing hypertension.

As a result of many years' investigation, much of which has been previously reported, Dieckmann feels that the latter two possibilities are unlikely and that it is most probable that the lesion is not peculiar to pre-eclampsia but may also be found in some patients with hypertensive disease. If this is correct it must then be assumed that the lesion is secondary rather than the primary factor. It has been suggested earlier that the narrowing and blockage of the glomerular capillaries are responsible for the symptoms in pre-eclampsia, but if the lesion is also found in hypertensive disease this seems improbable.

We may conclude that this disturbance in the glomeruli occurs much more commonly in primiparas with symptoms of toxemia than in multiparas with similar symptoms; that it is most frequent in women who warrant a diagnosis of pre-eclampsia, but that it may also occur in hypertensive toxemia also.

Summary

Renal biopsies were obtained from 26 primiparas and 44 multiparas during or at the termination of pregnancy and in one nonpregnant multipara.

A moderate or severe change (2+ or 3+) in renal glomeruli consisting of thickening of basement membrane, the presence of fibrils in endothelial cells, and narrowing of glomerular capillaries was present in all of 11 primiparas with a clinical diagnosis of pre-eclampsia, in 2 of 3 with eclampsia, and in 5 of 7 with a diagnosis of hypertensive disease. It was also present in 6 of 26 multiparas with a diagnosis of hypertensive disease.

It is concluded that this lesion may occur in patients with any variety of toxemia of pregnancy but that it is most constant in primiparas with a diagnosis of pre-eclampsia. There is no evidence that it persists to be responsible for permanent kidney damage.

A mild change (1+), consisting of slight thickening of basement membrane, slight fibrillation in endothelial cells, and little reduction in capillary lumina, was found in one primipara with eclampsia, 3 with a clinical diagnosis of

glomerulonephritis, and in 13 multiparas with a diagnosis of hypertensive disease, and 4 with normal pregnancies. It is concluded that this mild a lesion rarely occurs in pre-eclampsia but is moderately frequent in multiparas with hypertensive disease.

We are grateful to the various members of the staff, especially Dr. John Harrod, who obtained biopsies at operations.

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THE EFFECT OF BENEMID ON URIC ACID EXCRETION IN NORMAL PREGNANCY AND IN PRE-ECLAMPSIA

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ELEVATED blood levels and impaired urinary excretion of uric acid are frequently observed in patients with pre-eclampsia. According to Chesley[5] the renal clearance of uric acid in toxemia of pregnancy is decreased because of an increased reabsorption of uric acid in the proximal tubules. Others[4, 10] have suggested that the concomitant depression of the glomerular filtration rate is a major factor in the decreased renal clearance. The changes in uric acid metabolism presumed to be characteristic of pre-eclampsia are not always present. The blood level for instance does not always correlate with the measured renal clearance; patients with pre-eclampsia often have normal blood levels in spite of depressed renal clearance. Also, the severity of the disease does not coincide with either the degree of hyperuricemia or the depression in uric acid clearance.

Since so many factors are involved in determining the blood level of uric acid, it is difficult to evaluate the contribution of a single one. An abnormality may exist in uric acid production, in renal excretion, in uricolysis, or even in metabolism of uric acid from nucleic acids. Other important considerations are the state of hydration and muscular activity; labor and nonspecific convulsions, for instance, will produce hyperuricemia.[6, 7]

In an attempt to evaluate to some degree the function of the kidney in the production of hyperuricemia in toxemia of pregnancy, we have administered a uricosuric agent, Benemid,* to normal pregnant women and to patients with various forms of "toxemia." Benemid, p-(di-n-propylsulfamyl)-benzoic acid, prevents tubular reabsorption of uric acid and has been used effectively in the management of chronic gout.[9, 13] Pitts and Chambers,[12] studying normal nonpregnant subjects with Benemid, found a 42 per cent decrease in the blood uric acid level accompanied by a 72 per cent increase in urinary excretion per 24 hours. Benemid also blocks renal tubular excretion of penicillin and para-amino salicylic acid.

Material

Fourteen patients were studied. Five patients whose pregnancies were uncomplicated by any evidence of pregnancy toxemia served as *normal controls.* Three patients with *fluid retention* had an abnormal gain in weight associated with pitting edema; none had hypertension or proteinuria. Four pa-

*The Benemid was supplied by Sharp & Dohme, West Point Division, through the courtesy of Dr. Richard Smith.

tients had *pre-eclampsia* with hypertension, proteinuria, and edema beginning late in pregnancy; 3 were considered to have severe and one mild pre-eclampsia. One patient with previous known hypertension developed *superimposed acute toxemia* with increased hypertension, proteinuria, and excessive weight gain. Another patient had long-existing *chronic nephrosis.*

Method

The blood uric acid levels and total 24 hour urinary excretions of uric acid were measured daily during the period of study by the direct method of Folin and Wu. After a control period of one or more days Benemid was given orally in a total dosage of 2.0 Gm. daily (0.5 Gm. every 6 hours starting at 6:00 A.M.) for three days. The fasting blood samples were drawn between 8:00 and 9:00 A.M. Each patient ate a regular hospital diet during the test period. No medication of any kind was administered but an attempt was made to maintain the daily fluid intake at a constant level to assure a relatively constant and adequate output of urine.

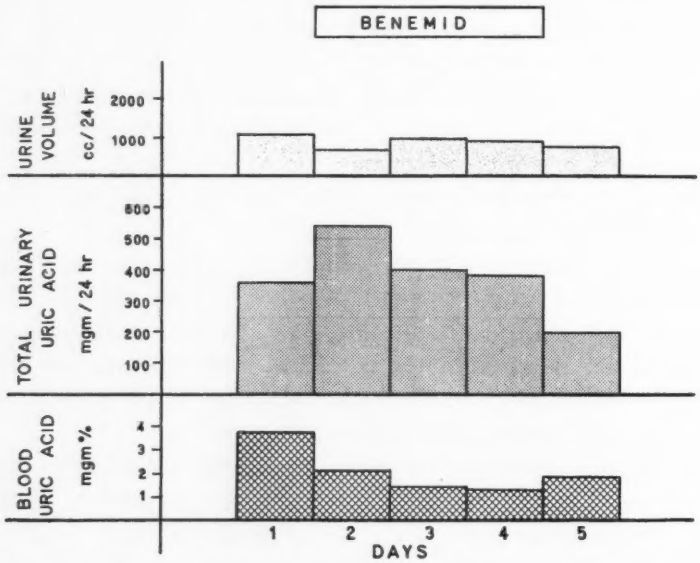


Fig. 1.—E. B., 31 years old, gravida v, para iii. Normal pregnancy at thirty-eighth week.

Results

Normal Patients.—The 24 hour urinary excretion of uric acid during the control period averaged 490 mg. per 24 hours with a range of 290 to 720 mg. Benemid produced a marked increase in urinary excretion; the greatest uricosuric effect was observed during the first 48 hours of therapy (Fig. 1). At the peak of uricosuric effect the excretion averaged 883 mg. per 24 hours, representing an increase of 80 per cent. In some cases the actual uricosuria exceeded 100 per cent of the initial values per 24 hours. The urinary output remained fairly constant throughout the study period.

In one patient Benemid was continued for six days and the uricosuric effect was demonstrable during the entire period of treatment (Fig. 2). The maximum excretion of uric acid was noted during the second 24 hours of Benemid therapy.

The average pretreatment blood level was 4.8 mg. per cent with a range of 3.2 to 5.0 mg. per cent. The average blood uric acid at the lowest point during therapy was 2.1 mg. per cent; representing a fall of 56 per cent

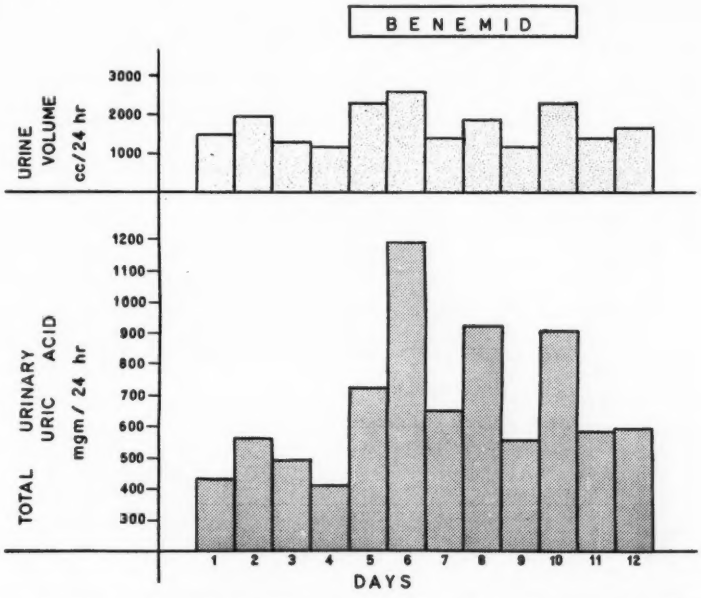


Fig. 2.—M. B., 39 years old, gravida vi, para v. Normal pregnancy at thirty-second week

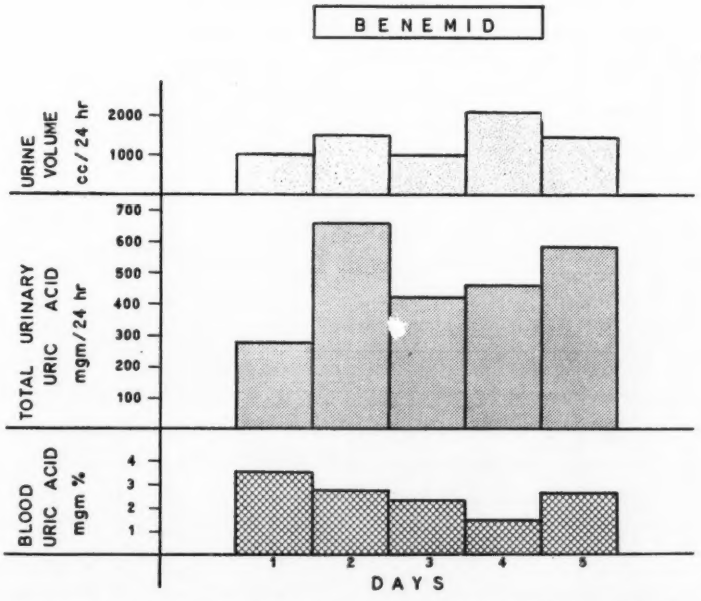


Fig. 3.—M. M., 26 years old, gravida ii, para 0. Fluid retention at thirty-ninth week.

(Fig. 1). The lowest blood level of uric acid usually coincided with the maximum uricosuric effect. The blood level returned to the pretherapy level within one to two days. In one patient the blood level was higher after administration of Benemid.

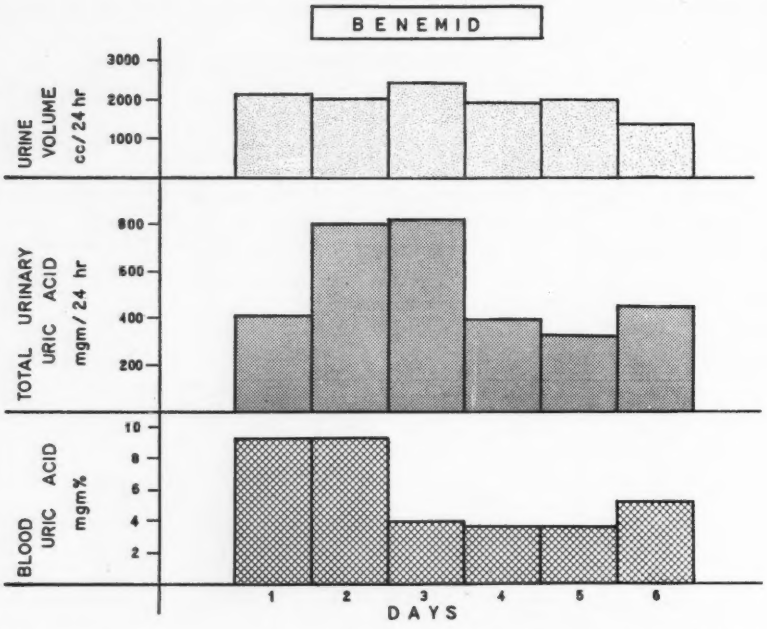


Fig. 4.—D. C., 19 years old, gravida i, para 0. Severe pre-eclampsia at thirty-eighth week.

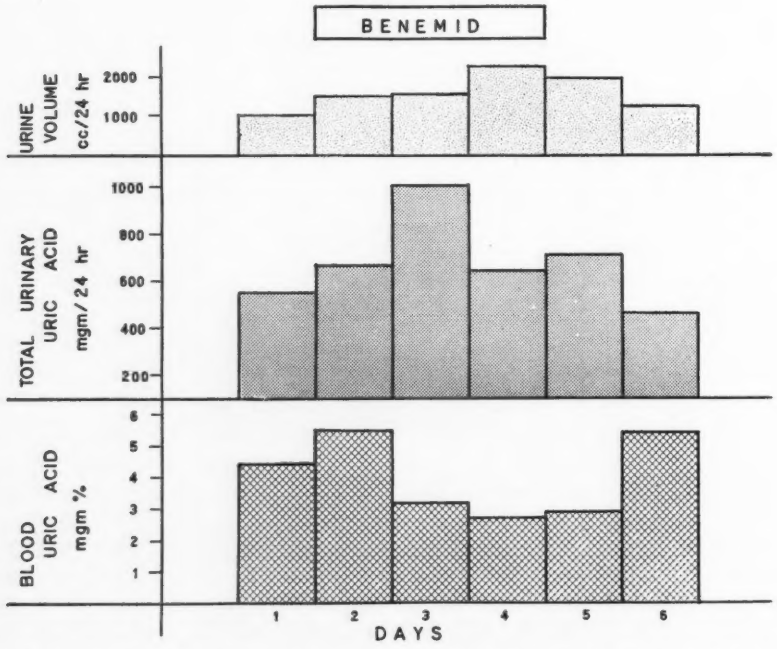


Fig. 5.—S. W., 24 years old, gravida i, para 0. Essential hypertension with superimposed acute toxemia at thirty-first week.

Fluid Retention.—The results in this group closely resemble those obtained in the normal patients. The urinary excretion of uric acid during the control period averaged 445 mg. per 24 hours. The initial blood level averaged 4.0 mg. per cent. At the height of the uricosuric effect the urinary excretion of uric acid increased 91 per cent. This was accompanied by a 67 per cent fall in blood uric acid (Fig. 3).

Pre-eclampsia.—The most dramatic results were seen in the 3 patients with severe pre-eclampsia. The uric acid excretion during the control period averaged 420 mg. per 24 hours. At the peak of uricosuria the excretion averaged 1,150 mg. per 24 hours, an increase of 173 per cent (Fig. 4). In one patient the excretion of uric acid exceeded 200 per cent of the initial value per 24 hours. The daily excretion of urinary protein did not change during the course of therapy and the urine volume remained fairly constant throughout the period of study.

The blood uric acid averaged 8.6 mg. per cent during the control period and fell to 3.7 mg. per cent during treatment, a decrease of 57 per cent. In spite of such a remarkable fall in blood uric acid levels, the clinical course of pre-eclampsia was not altered.

In the one patient with mild pre-eclampsia the control urinary uric acid excretion of 602 mg. per 24 hours increased to a maximum of 808 mg. per 24 hours, an increase of 34 per cent. The blood uric acid decreased from 6.0 mg. per cent to 3.6 mg. per cent, a fall of 40 per cent.

Essential Hypertension With Superimposed Acute Toxemia.—The urinary uric acid excretion increased from 550 mg. per 24 hours during the control period to 1,000 mg. per 24 hours, an increase of 82 per cent. This was accompanied by a decrease of blood uric acid from 4.4 mg. per cent to 2.8 mg. per cent, a fall of 36 per cent. No clinical improvement was detected (Fig. 5).

Chronic Nephrosis.—Although there was a slight increase in urine volume on the first day of therapy, this subject displayed no response to Benemid therapy. Similar lack of response has been noted previously when Benemid was administered to nonpregnant patients with diseased kidneys.[11]

Comment

Innumerable factors may regulate uric acid excretion in pregnancy. ACTH is an effective uricosuric agent[2] but just what part adrenal steroids and other hormones play in uric acid excretion during normal and abnormal pregnancy has not been determined. Since there is increased production of steroids in normal pregnancy with alterations in various fractions in pregnancy toxemia,[8, 14] one might assume that there are additional factors operating in pregnancy and in the toxemias of pregnancy to control uric acid excretion. The renal disposition of uric acid therefore must represent only a part of the entire body mechanism for uric acid excretion; the renal factor must be still more clearly defined in both normal and "toxemic" pregnancies.

The increased excretion of uric acid in response to Benemid administered to normal pregnant women and those with fluid retention was not unexpected. In the normal individual uric acid is completely filtered through the glomeruli and 85 per cent of it is reabsorbed in the proximal tubules[3]; therefore, if an effective block is provided at the level of the renal tubules, a definite uricosuric effect must occur. The patients with fluid retention display minimal renal dysfunction as measured by other renal function tests and therefore one would expect a response similar to that in the normal pregnant patients.

The greater uricosuric effect in the patients with severe pre-eclampsia does not necessarily indicate that the high blood levels are due to increased reabsorption in the proximal tubules. There certainly is a greater amount of uric acid to be eliminated in pre-eclamptic patients but hyperuricemia of pre-eclampsia may be the result of metabolic as well as of renal dysfunction.

The degree of uricosuria obtained with Benemid in the toxemic patients probably indicates an enlarged metabolic pool of uric acid. The amount of uric acid in the body must, however, be smaller than that characteristically seen in gouty patients,[1] since it is impossible to lower the blood level so drastically in the latter. The rapid return of the blood level to the pre-treatment level probably indicates an increased production or "turn-over rate" of uric acid in normal pregnancy and in toxemia of pregnancy.

If the elevated blood levels of uric acid were of some significance in the etiology of pre-eclampsia, one might expect clinical improvement with Benemid therapy. Such an improvement was not witnessed during the study. We may presume from this that hyperuricemia is primarily the result of the metabolic dysfunction produced by toxemia of pregnancy rather than a cause.

Results similar to those in women with pre-eclampsia were obtained in the hypertensive patient with superimposed acute toxemia but here also the clinical picture was not altered by lowering the blood uric acid level.

Summary

Benemid, a uricosuric agent, was given orally to fourteen pregnant patients. Uricosuria was obtained in both normal pregnant and toxemia patients. The uricosuric effect was greatest in the toxemia of pregnancy and was accompanied by a rapid fall in blood level. No clinical change was observed among the patients studied, and apparently hyperuricemia alone is not an important causative factor in pregnancy toxemia. There was no response to Benemid therapy in a pregnant patient with chronic nephrosis.

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URIC ACID AND ENDOGENOUS CREATININE CLEARANCES AFTER NORMAL AND TOXEMIC PREGNANCY

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RENAL clearance studies during the immediate and late postpartum periods in normal women and in those who have had pregnancy toxemia have shown varying results. Many investigators reported that the depressed renal clearances of inulin, Diodrast, and creatinine in patients with toxemias of pregnancy return to normal during the first postpartum week. Others have found the renal function to be significantly depressed during the postpartum period, especially in patients with residual hypertension.

If pregnancy has been uncomplicated, the renal blood flow and glomerular filtration return soon after delivery to levels characteristic of those in nonpregnant women. Wellen, Welsh, and Taylor,[1] however, found diminished Diodrast clearances and elevated inulin clearances in 13 recently delivered patients who had had toxemia during pregnancy. Similar results were observed by Kariher and George[2] in patients studied after the twelfth postpartum day. A later study by Wellen, Welsh, and Taylor[3] of tests performed on patients with essential hypertension one to four years after delivery showed no alterations of glomerular filtration rate, effective renal blood flow, and tubular excretory mass. Corcoran and Page[4] repeatedly studied 20 patients with late toxemia of pregnancy from 2 to 1,092 days post partum. In those whose hypertension persisted after delivery they found a decreased renal blood flow with some increase in filtration fraction; the normotensive patients showed normal renal function.

Dill, Isenhour, Cadden, and Schaffer[5] studied the glomerular filtration rate and renal blood flow in normal pregnant women and patients with pre-eclampsia or essential hypertension. Single studies during the immediate postpartum period showed normal glomerular filtration rates with decreased renal blood flow in both pre-eclamptic and hypertensive patients. The same investigators[6] studied 6 pregnant patients who had had acute toxemia of pregnancy one to five years previously and 9 additional nonpregnant patients with a history of acute toxemia of pregnancy six months to twelve years previously. Inulin clearances in the nonpregnant women were depressed in direct proportion to the time elapsed since the toxemic pregnancy; no normal values were obtained in patients who were more than one year post partum. In this posttoxemia group the renal blood flow was depressed with a normal filtration fraction and the uric acid clearance was normal. In the pregnant women at term the renal

blood flow was minimally depressed and the filtration fraction was normal. Postpartum studies revealed a slightly depressed inulin clearance and moderately depressed Diodrast clearance.

Chesley and associates[7] obtained normal values for Diodrast clearance before and after delivery in patients with varying degrees of toxemias. Odell[8] noted gradual increases in clearances of inulin, exogenous creatinine, and urea during the immediate postpartum period. Chesley[9] in his extensive study of simultaneous renal clearances of urea and uric acid in normal patients and patients with toxemia found a rapid return to normal values with single clearance tests performed during the immediate postpartum period. Similar results were reported by Bonsnes and Stander,[10] employing the 24 hour clearance technique of uric acid and urea.

Dieckmann[11] noted gradual improvement of renal clearance of urea following toxemic pregnancy and attributed this to a possible hypertrophy of kidney tissue or decreased arteriolar spasm of the renal vessels. He recommended serial kidney function tests during the postpartum period. Bucht and Werkö[12] have reported a return to near normal values of the glomerular filtration rate and renal plasma flow in postpartum studies performed one to two years after delivery.

We have undertaken the present study of normal and toxemic patients to determine whether there are changes in the renal clearance of uric acid and creatinine during the immediate and late postpartum periods. The method and the results of the same studies in undelivered women have been reported in a previous communication.[13]

Material

Between September, 1952, and September, 1954, 118 simultaneous uric acid and endogenous creatine clearance studies were performed on 75 postpartum patients. The majority were ward patients from the Obstetric Clinic of the Temple University Hospital, but a few were private patients whose pregnancies had been complicated by acute toxemia or severe hypertension.

Because the greatest fluctuations in renal clearance values appear to occur during the first ten days of the puerperium the studies were arbitrarily divided into those performed *early* (within 10 days of delivery) and those performed *late* (from 10 to 227 days after delivery). The initial study was made before the patient left the hospital after delivery and the first subsequent test was usually made from three to six weeks later. A few patients were studied three or four times.

Eight normal patients whose pregnancies had been uncomplicated and who were delivered without difficulty served as *normal controls*. The 19 patients with *pre-eclampsia* had been normal before conception and during the early period of gestation, but all developed characteristic signs of toxemia as pregnancy advanced. In each of the 6 with *essential hypertension* the blood pressure was elevated before conception or during the first half of the pregnancy. None had edema or proteinuria. The 9 with *essential hypertension with superimposed acute toxemia* were patients with previous hypertension in whom an acute process, characterized by edema, proteinuria, and further rise in blood pressure, appeared during the pregnancy. The highest blood pressures and the greatest amounts of proteinuria were found in this group. The patients with *fluid retention* had gained an excessive amount of weight because of the accumulation of fluid in the tissues but none had proteinuria or a change in blood pressure.

Results

Normal.—The uric acid clearance before delivery averaged 13.0 c.c. per minute. It was 13.9 c.c. per minute during the first ten days after delivery and 15.0 c.c. per minute when the same patients were studied later (Table I). This was accompanied by a rise in endogenous creatinine clearance from 105 c.c. per minute during the early puerperium to 134 c.c. per minute (Table II). The average antepartum creatinine clearance was 108 c.c. per minute.

The blood uric acid which averaged 3.0 mg. per cent before delivery fell from an immediate postpartum level of 4.9 mg. per cent to 3.9 mg. per cent (Table III). This is in accordance with Crawford's[14] observation of increasing levels of blood uric acid with labor. The consistency of normal blood values is reflected in the small standard deviation. All blood determinations after the tenth postpartum day were less than 5.0 per cent.

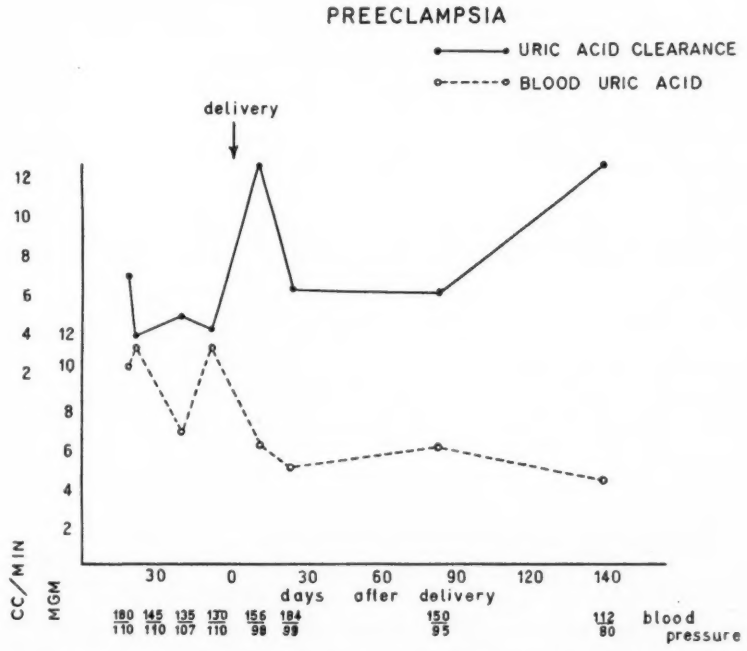


Fig. 1.—J. G., 30 years old, gravida i, para 0. Severe pre-eclampsia. Delivered by cesarean section at 32 weeks.

Pre-eclampsia.—The uric acid clearance in late pregnancy averaged 6.5 c.c. per minute. During the immediate puerperium it rose to an average of 14.5 c.c. per minute with a range of 8.8 to 31.3 c.c. per minute. During the late puerperium it fell to 10.6 c.c. per minute with a range of 3.9 to 23.6 c.c. per minute (Table I). In some patients the clearance returned to normal levels fairly promptly while in others it remained depressed for weeks. (Fig. 1.)

The blood levels of uric acid averaged 6.0 mg. per cent before delivery, 5.0 mg. per cent during the immediate puerperium, and 4.6 mg. per cent later (Table III).

The endogenous creatinine clearance averaged 99.0 c.c. per minute before delivery. There was an increase to 112 c.c. per minute during the immediate puerperium and to 123 c.c. per minute later. In most patients the excretion of creatinine tended to follow that of uric acid, the clearance remaining low in those whose uric acid clearances are reduced.

TABLE I. POSTPARTUM URIC ACID CLEARANCE

DIAGNOSIS	LESS THAN 10 DAYS POST PARTUM: AVERAGE CLEARANCE (C.C./MIN.)	RANGE	NO. OF PATIENTS	MORE THAN 10 DAYS POST PARTUM: AVERAGE CLEARANCE (C.C./MIN.)	RANGE	NO. OF PATIENTS
Normal	13.9 (± 6.0)*	7.6-27.8	8	15.0 (±7.1)	9.7-28.8	7
Pre-eclampsia	14.5 (±12.8)	8.8-31.3	19	10.6 (±4.8)	3.9-23.6	15
Essential hypertension	16.1 (± 6.7)	7.9-29.2	6	14.0 (±6.7)	9.9-21.2	7
Essential hypertension with superimposed toxemia	12.4 (± 6.3)	3.2-26.5	9	12.7 (±6.7)	4.1-27.7	9
Fluid retention	14.5 (± 7.4)	4.7-25.1	17	10.9 (±0.8)	9.6-11.8	4

*Figures in parentheses based on standard deviation.

TABLE II. POSTPARTUM ENDOGENOUS CREATININE CLEARANCE

DIAGNOSIS	LESS THAN 10 DAYS POST PARTUM: AVERAGE CLEARANCE (C.C./MIN.)	RANGE	NO. OF PATIENTS	MORE THAN 10 DAYS POST PARTUM: AVERAGE CLEARANCE (C.C./MIN.)	RANGE	NO. OF PATIENTS
Normal	105 (±42)	52-175	8	134 (±25)	88-170	7
Pre-eclampsia	112 (±28)	55-153	17	123 (±56)	69-210	14
Essential hypertension	112 (±38)	67-169	5	124 (±49)	65-170	7
Essential hypertension with superimposed toxemia	118 (±46)	56-200	9	94 (±45)	62-227	8
Fluid retention	93 (±24)	71-160	17	118 (±28)	77-151	4

TABLE III. POSTPARTUM BLOOD URIC ACID

DIAGNOSIS	LESS THAN 10 DAYS POST PARTUM: AVERAGE (MG.%)	RANGE	NO. OF PATIENTS	MORE THAN 10 DAYS POST PARTUM: AVERAGE (MG.%)	RANGE	NO. OF PATIENTS
Normal	4.9 (±1.2)	2.4-6.4	8	3.9 (±0.6)	2.8-4.6	7
Pre-eclampsia	5.0 (±1.3)	2.2-6.4	19	4.6 (±1.1)	3.0-7.6	15
Essential hypertension	4.5 (±1.2)	3.0-6.3	6	3.9 (±1.8)	2.6-8.0	7
Essential hypertension with superimposed toxemia	5.5 (±1.6)	3.0-8.0	9	4.3 (±1.5)	2.2-7.2	9
Fluid retention	4.8 (±1.2)	3.8-7.0	17	5.0 (±0.8)	4.2-6.4	4

Essential Hypertension.—The average uric acid clearance which had been 14.2 c.c. per minute during pregnancy was 16.1 c.c. per minute during the immediate puerperium with a range of 7.9 to 29.2 c.c. per minute. During the late puerperium it averaged 14.0 c.c. per minute with a range of 9.9 to 21.2 c.c. per minute (Table I).

The blood levels of uric acid averaged 4.1 mg. per cent during pregnancy, 4.5 mg. per cent during the immediate puerperium, and 3.9 mg. per cent later (Table III).

The creatinine clearance averaged 128 c.c. per minute during pregnancy, 112 c.c. per minute during the immediate puerperium, and 124 c.c. per minute later (Table II).

When compared to those in patients with pre-eclampsia, these postpartum clearances in women with uncomplicated essential hypertension are reasonably stable (Fig. 2).

Essential Hypertension With Superimposed Acute Toxemia.—The average uric acid clearance during late pregnancy was 4.5 c.c. per minute. During the immediate puerperium it averaged 12.4 c.c. per minute with a range of 3.2 to 26.5 c.c. per minute. During the late puerperium it averaged 12.7 c.c. per minute with a range of 4.1 to 27.7 c.c. per minute.

The blood levels of uric acid averaged 5.6 mg. per cent during pregnancy, 5.5 mg. per cent during the immediate puerperium, and 4.3 mg. per cent later (Table III).

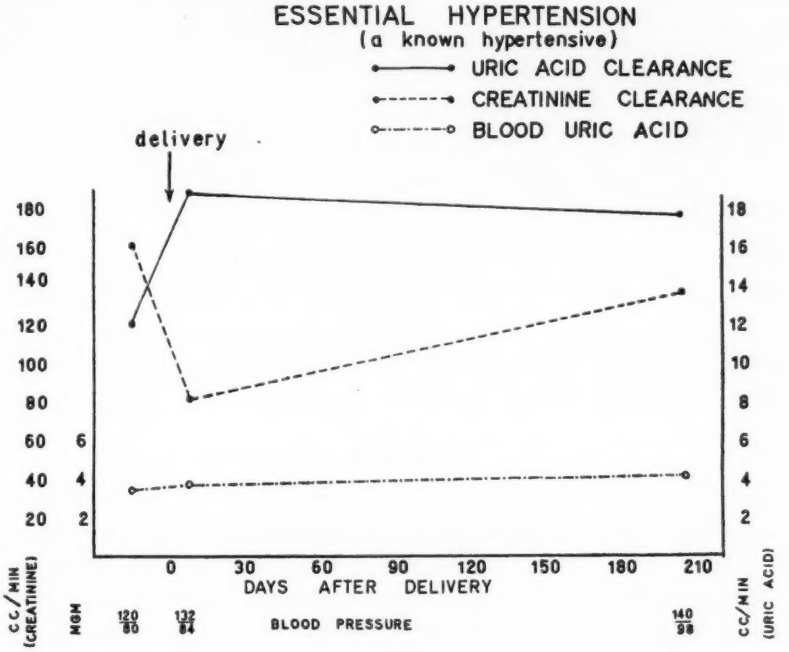


Fig. 2.—L. J., 27 years old, gravida v, para iv. Known hypertensive patient from previous deliveries. Term delivery.

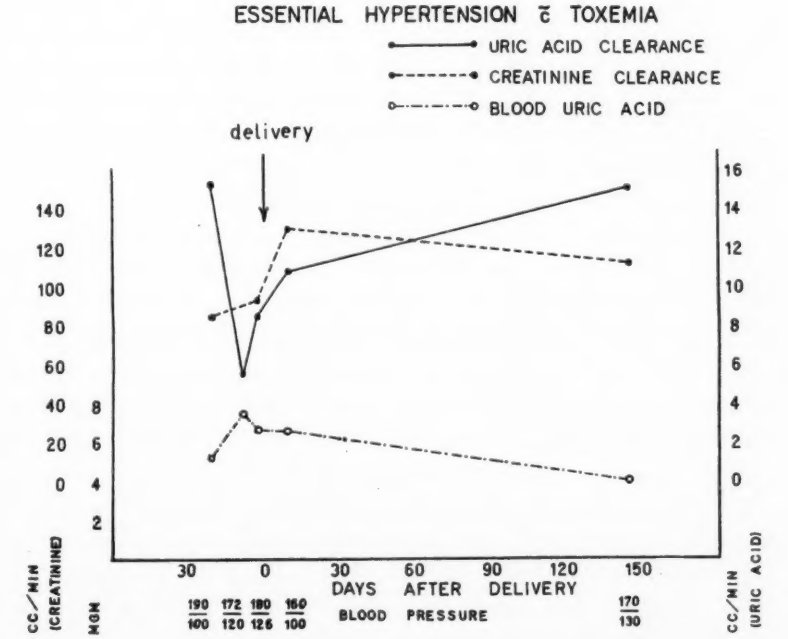


Fig. 3.—I. G., 40 years old, gravida iv, para iii. Essential hypertension with severe superimposed toxemia. Delivered at 28 weeks.

The endogenous creatinine clearance averaged 60 c.c. per minute during pregnancy and 118 c.c. per minute during the immediate puerperium but fell to 94 c.c. per minute later (Table II).

The lowest creatinine clearances were found in these patients and while the average figure for uric acid clearances is within the normal range it is somewhat lower than those found in the normal women and the ones with uncomplicated essential hypertension (Fig. 3).

Fluid Retention.—The average uric acid clearance during pregnancy was 11.1 c.c. per minute. During the immediate puerperium it averaged 14.5 c.c. per minute with a range of 4.7 to 25.1 c.c. per minute and during the late puerperium it averaged 10.9 c.c. per minute with a range of 9.6 to 11.8 c.c. per minute (Table I).

The blood uric acid levels averaged 4.5 mg. per cent during pregnancy, 4.8 mg. per cent during the immediate puerperium, and 5.0 mg. per cent later (Table III).

The endogenous creatinine clearance averaged 110 c.c. per minute during late pregnancy, 93.0 c.c. per minute during the immediate puerperium, and 118 c.c. per minute later (Table II).

Comment

The renal excretion of uric acid and creatinine during the puerperium varied considerably in the patients examined in this study. The first few days represent a period of adjustment with rapid changes in general metabolism and in kidney function and it is not surprising that the results of the tests varied widely even in women presumed to have similar conditions complicating pregnancy.

The patients with acute toxemias of pregnancy displayed the greatest fluctuation of renal clearances suggesting that they had experienced the greatest derangement of renal physiology. The abrupt increase in the clearances of uric acid during the first few days after delivery may represent the increased excretion of the excess uric acid so often present in women with pre-eclampsia. The range of uric acid clearance (8.8 to 31.3 c.c. per minute) probably is the result of variations in amounts and distribution of retained fluid, height of blood pressure, predelivery renal function, and a number of other factors which could not be controlled in this study. The creatinine clearances were higher than in the normal controls during the early puerperium but later were all reduced although still within normal range. Somewhat similar but less pronounced changes were observed in patients with acute toxemia superimposed upon chronic hypertension and in patients with unusual fluid retention.

There was much less variation in uric acid and creatinine clearances in the patients with uncomplicated essential hypertension and in the normal controls. In the latter, postdelivery renal function appeared to be unaffected by pregnancy. The late creatinine clearances in hypertensive women, however, were somewhat lower than these in normal controls despite the fact that increased glomerular filtration is regarded by many investigators as being characteristic of this condition in its early stages. Unfortunately, we have no information concerning prepregnancy function in these women; consequently, we cannot determine whether kidney activity was altered by the pregnancy studied.

It seems certain from this and other studies that the true state of kidney activity cannot be evaluated by a single test of renal function performed soon after delivery. This seems to be particularly true of the uric acid clearance which may be unusually high because of the necessity of eliminating the excess uric acid produced during the predelivery period. Repeated tests at later dates may show reduced activity even though the blood pressure has fallen to a normal or near normal level. It was impossible to differentiate patients with mild pre-eclampsia from those in whom the condition was more severe by postdelivery studies of uric acid and endogenous creatinine clearances. This is also true during the active stages of pre-eclampsia, but creatinine clearance is more apt to be altered before delivery than is the clearance of uric acid.

If one wishes to attempt to evaluate the effects of a given pregnancy on renal function, the tests should be performed not only during the first week after delivery but also six months and one year later. This should provide a reasonably accurate indication of what has happened, particularly if the functional status had been checked before the pregnancy.

Summary

Seventy-five patients with normal pregnancy, pre-eclampsia, fluid retention, and chronic hypertension with and without superimposed acute toxemia were studied during the puerperium with uric acid and endogenous creatinine clearance tests. The initial tests were done during the first 10 days after delivery and succeeding tests were done from 11 to 227 days after delivery. Great variations were found in both uric acid and creatinine clearances during the early puerperium. The normal control and fluid retention groups showed minimal changes during the postpartum period while the greatest changes were found among the women who had had pre-eclampsia and essential hypertension with superimposed acute toxemia. In many patients who had had pre-eclampsia the clearances during the early puerperium were normal or increased but when the same patients were studied two to four weeks later, the function was decreased. A gradual return to normal clearance was often observed over a period of from two to seven months.

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HYPERTONIC SALINE INFUSIONS FOR THE DIFFERENTIAL DIAGNOSIS OF THE TOXEMIAS OF PREGNANCY

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THE positive fluid balance which is characteristic of normal pregnancy is exaggerated in patients who develop pre-eclampsia-eclampsia and many of the physiologic disturbances which accompany the latter condition may be in part due to edema. Zangemeister[5] first suggested that abnormal water retention caused "hydrops gravidarum," which he regarded as a precursor of the convulsions of eclampsia. Fink[3] considered the cause of edema in normal pregnancy to be an excessive intake of salt and acid foods. Harding and Van Wyck[4] observed increased edema, weight, proteinuria, and hypertension in patients with pre-eclampsia after the oral administration of sodium salts. In 1950, Dieckmann and his co-workers[1] reported that repeated intravenous injections of hypertonic sodium chloride solutions produced marked increases in blood pressure, weight, and urinary protein excretion in patients with pre-eclampsia. Advance in the severity of pre-eclampsia did not occur, however, when sodium lactate solutions were injected in patients on low chloride diets. The authors postulated that an adequate amount of chloride ion must be present before excessive sodium can affect the course of pre-eclampsia. Dieckmann, Pottinger, and Rynkiewicz[2] subsequently described a test based upon the measurement of urinary sodium and chloride excretion after the injection of concentrated saline solution, which they believe will aid in differentiating pre-eclampsia from other similar abnormalities in pregnant women.

It is often difficult to make an accurate clinical differentiation between the "toxemias" of pregnancy even though definite criteria for their evaluation have been established. A test by which one could separate pre-eclampsia from other similar conditions would make diagnosis easier and more accurate and might at the same time serve as a prognostic guide when early or equivocal stages of the disease are recognized. Because an evaluation of the Dieckmann Salt Test has not as yet been reported from a clinic other than that in which it was originated, this study was undertaken in an attempt to determine whether it could be used as a practical aid to the clinician in diagnosing pre-eclampsia.

Method and Materials

Salt tests were administered to 213 pregnant women being cared for in the Department of Obstetrics and Gynecology of the Temple University Hospital. These were performed in 62 patients with pre-eclampsia, in 41

with uncomplicated essential hypertension, 20 with essential hypertension and superimposed acute toxemia, 53 with fluid retention, 1 with acute glomerulonephritis, and 3 with chronic glomerulonephritis; 33 others served as normal controls.

The patients with *pre-eclampsia* were almost all young primigravidas, all had been normal before pregnancy and during at least the first 20 weeks of the gestational period; all eventually developed edema, proteinuria, and abnormally elevated blood pressures. The patients with *essential hypertension* were all known to have had blood pressure elevations before conception or during the first 20 weeks of pregnancy. The patients with *essential hypertension and superimposed acute toxemia* all were known to have had hypertension before the onset of pregnancy and in each an acute process characterized by edema, proteinuria, and a rising blood pressure developed as pregnancy advanced. The patients with *fluid retention* had all gained weight excessively due to an abnormal accumulation of body water. None had either an increased blood pressure or an abnormal urinary protein excretion at any time during pregnancy, labor, or the puerperium.

The tests were performed on hospitalized patients usually within 48 hours of their admittance. In a few cases of fluid retention the tests were done on the women as outpatients. Breakfast was withheld on the morning of the test but until that time the patients, with few exceptions, were maintained on their normal diets at home or on a hospital house diet which provides 6 to 9 Gm. of sodium chloride and about 3 Gm. of potassium. Each of the hospitalized patients ingested between 2 and 3 L. of fluid daily and all were encouraged to remain out of bed until the tests had been performed. In most instances, however, the patients spent more time in bed than they had before entering the hospital. The inpatients were weighed at the same time each morning, including the test day, and six hours after the completion of the test. Outpatients were either admitted the night before the test or early on the morning of the test day but otherwise the procedure was similar to those performed on inpatients.

Immediately preceding the test the bladder was emptied through a mushroom catheter which was left in place during the study. One liter of 2.5 per cent sodium chloride was injected intravenously within a period of 30 to 40 minutes. The bladder was again emptied 15 minutes after the completion of the intravenous injection and the specimen of urine was discarded. All the urine passed during the next two hours was collected and measured, and its sodium and chloride contents were determined.

The blood pressure and pulse rates were recorded before the injection was begun, every 5 minutes during the injection, and every 15 minutes for at least an hour after the completion of the test.

Results

Electrolyte Excretion:

Normal pregnancy: In 33 tests on normal patients 32 to 40 weeks pregnant, the mean value for urinary sodium concentration was 267 (±40) meq. per liter, and the total sodium excretion averaged 60 (±26) meq. The mean value for urinary chloride concentration in 13 patients was 286 (±53) meq. per liter, and the total chloride excretion averaged 57 (±20) meq. (Table I).

Pre-eclampsia: The salt test was administered to 62 patients with pre-eclampsia: 45 times in women with mild toxemia and 17 with severe. The mean value for the urinary sodium concentration for the entire group was 158 (±42) meq. per liter and the total chloride excretion averaged 36 (±21) meq.

TABLE I

DIAGNOSIS	URINARY SODIUM					URINARY CHLORIDE				
	CONCENTRATION (MEQ./L.)			TOTAL MEQ.		CONCENTRATION (MEQ./L.)			TOTAL MEQ.	
	NO.	MEAN	RANGE	MEAN	RANGE	NO.	MEAN	RANGE	MEAN	RANGE
Normal pregnancy	33	267	227-307	60	34-86	13	286	233-339	57	37-77
Pre-eclampsia:										
Total	62	158	102-214	47	18-76	37	126	84-168	36	15-72
Mild	45	209	159-259	48	22-74	27	132	93-171	38	18-58
Severe	17	137	75-199	43	7-79	10	117	80-154	28	4-52
Essential hypertension	41	226	189-263	67	34-100	18	194	150-238	43	22-64
Essential hypertension with superimposed toxemia	20	172	136-208	87	43-131	13	193	152-386	99	52-146
Fluid retention	53	240	190-290	63	36-90	18	183	124-242	54	35-73
Nephritis:										
Acute	1	122		49		1			49	
Chronic	1	194		87		1			77	
Chronic	1	181		58		1			53	
Chronic	1	140		61		1			50	

TABLE II

DIAGNOSIS	URINARY SODIUM					URINARY CHLORIDE				
	CONCENTRATION (MEQ./L.)			TOTAL MEQ.		CONCENTRATION (MEQ./L.)			TOTAL MEQ.	
	NO.	MEAN	RANGE	MEAN	RANGE	NO.	MEAN	RANGE	MEAN	RANGE
Fluid retention. No subsequent pre-eclampsia	53	240	190-290	63	36-90	18	183	124-242	54	35-73
Fluid retention. Subsequent pre-eclampsia	31	181	136-226	52	25-79	17	136	97-175	46	26-66
Pre-eclampsia	62	158	102-214	47	18-76	37	126	84-168	36	15-72

The patients with severe pre-eclampsia tended to have lower electrolyte excretion values than did those with mild pre-eclampsia but because there was considerable overlapping, the test does not conclusively differentiate between the two (Table I).

Essential hypertension: Forty-one pregnant women with uncomplicated essential hypertension were studied. The mean value for the urinary sodium concentration was 226 (±37) meq. per liter and the total sodium excretion averaged 67 (±33) meq. The mean value for urinary chloride concentration in 18 was 194 (±41) meq. per liter and the total chloride excretion averaged 43 (±21) meq. (Table I).

Chronic hypertension with superimposed acute toxemia: Twenty women with benign essential hypertension who had developed superimposed acute toxemia were studied during the acute phase. The mean value for the urinary sodium concentration was 172 (±36) meq. per liter and the total sodium excretion averaged 87 (±44) meq. The figures for sodium concentration are similar to those obtained in patients with mild pre-eclampsia, but the total sodium excretion was even higher than that observed in normal pregnant women. The mean value for urinary chloride concentration in 13 was 193 (±41) meq. per liter and the total chloride excretion averaged 99 (±47) meq. (Table I).

Fluid retention: The mean urinary sodium concentration for the 53 women with fluid retention was 240 (±50) meq. per liter and the total sodium excretion averaged 63 (±27) meq. The mean value for urinary chloride concentration in 18 was 183 (±59) meq. per liter and the total chloride averaged 54 (±19) meq. (Table I).

Thirty-one additional patients were studied initially because of presumed fluid retention but each one subsequently developed signs and symptoms characteristic of pre-eclampsia. The results of the first tests which were run when the only obvious deviation from the normal was fluid accumulation, differed considerably from those in the 53 whose only evidence of abnormality throughout the entire pregnancy was edema. In the former the electrolyte excretion was similar to that of women with pre-eclampsia. The urinary sodium concentration was 181 (±45) meq. per liter and the total sodium excretion 52 (±27) meq. The urinary chloride concentration in 17 was 136 (±39) meq. per liter and the total chloride excretion was 46 (±20) meq. (Table II). Repeat tests, run after the typical signs of toxemia were obvious, are included in the group of 62 with pre-eclampsia.

Primary renal disease: The results obtained in one pregnant patient with acute glomerulonephritis and 3 with chronic glomerulonephritis are similar to those in women with pre-eclampsia (Table I). The test was repeated after delivery in 2 with chronic glomerulonephritis and the results were similar to those obtained during the antepartum study.

Clinical Observations.—

Blood pressure: Elevations in blood pressure of over 29 mm. Hg systolic were noted during the intravenous injections of the concentrated salt solution in 12 patients: 8 with unclassified toxemia, 2 with essential hypertension, and 2 with pre-eclampsia. The elevation persisted more than 12 hours only in the 2 with pre-eclampsia, but each had been given more than one salt test.

Weight and edema: In 13 normal pregnant women the average weight gain 6 hours after the test was 2.3 kilograms; the weight returned to the pretest level within 48 hours in 88 per cent and within 72 hours in 94 per cent. The average weight gain 6 hours after the test in 32 patients with pre-eclampsia was 2.5 kilograms, but the weight remained above the pretest level for at least 96 hours in 70 per cent of the patients. In 3 of the

patients with diagnoses of pre-eclampsia the weight returned to its original level within 24 hours after the completion of the test and 4 others had returned to the pretest weight within 48 hours. In 3, labor began within 24 hours of the performance of the test.

Proteinuria: No increase in urinary protein was observed during the initial salt test.

Exacerbation of pre-eclampsia: In one patient with mild pre-eclampsia the blood pressure rose after the third test within 5 days from 130/90 to 160/100 mm. Hg, where it remained until the sixth postpartum day. In another, acute pulmonary edema and a sharp increase in blood pressure occurred after 600 c.c. of the hypertonic solution had been administered. A progressive increase in severity of the signs of pre-eclampsia began one and two days following a single salt test in 2 other women whose toxemia had been stabilized for one and three weeks in the hospital.

Comment

A reasonably accurate diagnosis of pre-eclampsia can be made on the basis of the appearance and progression of abnormal clinical signs. Pre-eclampsia is usually characterized by an early excessive increment in weight which can be noted before hypertension and proteinuria appear; this becomes obvious early in the second half of pregnancy. Unfortunately, early and excessive weight gain, with or without edema, may also occur in patients who develop none of the other signs of toxemia and a few with pre-eclampsia evidence little or no edema. The practical value, therefore, of a procedure which would not only aid in diagnosing pre-eclampsia at an early stage but which, in addition, would indicate those patients with fluid retention who would subsequently develop toxemia is obvious.

Complete accuracy of any diagnostic test for pre-eclampsia would require a physiologic response to a stimulus which is consistent and different from that of normal pregnant women and those with other complications which are, at least superficially, similar to true pregnancy toxemia. Even though abnormalities in the metabolism of sodium and chloride are obvious in patients with pre-eclampsia, too little is known about the behavior of the electrolytes in healthy individuals to expect that an accurate diagnostic test can be based upon administration and excretion of these substances alone. The adequancy of renal function is difficult to assess without complicated tests which are not generally available and many factors which cannot be measured or which are at the present time unrecognized may be acting to alter electolyte metabolism.

In this study the results of the Dieckmann salt test corresponded with the clinical diagnosis in almost every patient thought to have pre-eclampsia. There is, however, overlapping of values for sodium excretion between those with pre-eclampsia and those in the other groups so that the salt test cannot be utilized alone to establish a diagnosis (Fig. 1). For instance, in a few of the patients with uncomplicated essential hypertension, a diagnosis of pre-eclampsia would have been made if only this test had been utilized and if the history, the physical examination, and the other laboratory findings

had been ignored. In addition, all of the patients with an acute process superimposed upon essential hypertension had salt excretion values within the range of those in pre-eclampsia. It is obvious that the test could not be utilized to differentiate between these two conditions. The test did, however, differentiate pre-eclampsia from normal pregnancy and from fluid retention in almost every instance.

If the disturbance in electrolyte metabolism actually is present during early pregnancy in the women who ultimately develop pre-eclampsia, the salt test should indicate the altered excretion before clinical signs appear. Of 84 patients with diagnoses relatively early in pregnancy of "fluid retention" because weight gain and edema were the only evidence of abnormality, the 31 in whom definite signs of pre-eclampsia became obvious 3 to 12 weeks later tended to have a salt excretion pattern similar to that in women with definite pre-eclampsia. The salt tests in the other 53 who did not develop pre-eclampsia were similar to those in normally pregnant women.

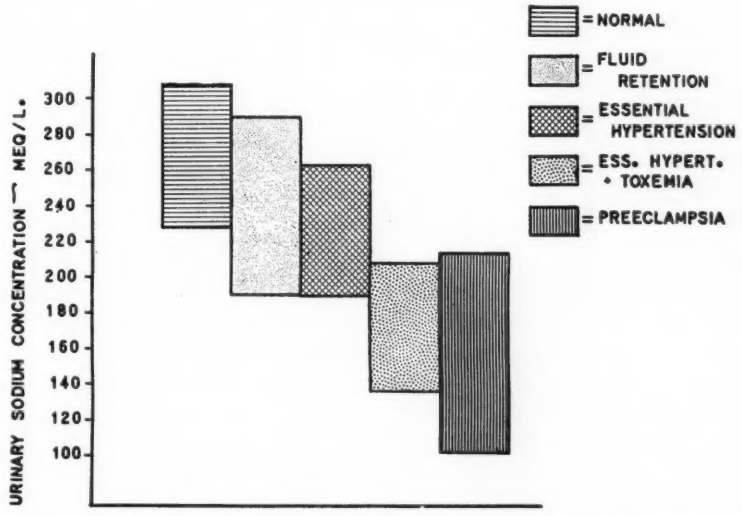


Fig. 1.—Comparative urinary sodium excretions after the injection of hypertonic saline solution.

The results of this study suggest that the Dieckmann salt test may prove to be more valuable as an aid in prognosis than as a method for pin-pointing the diagnosis in patients who already have developed toxemia of pr[illegible]ncy. It is not always possible to differentiate pre-eclampsia from fluid reten[illegible] alone during the period at which the only evidence of toxemia is excessive weight gain, but if further study confirms the findings suggested here, the salt test should be helpful in differentiating the two conditions and in planning treatment. The test can be performed safely in suspect patients; clinical signs of pre-eclampsia were never precipitated by a single salt test. Patients who are normal except for edema or an excessive increment of weight need be hospitalized only for 4 to 6 hours during the test but each should be examined 24 hours later to make certain that her condition is unchanged.

Summary

The Dieckmann salt test was performed in 213 pregnant women in an attempt to assess its diagnostic accuracy in differentiating the various toxemias of pregnancy from each other. On the basis of the test alone, pre-eclampsia, acute or chronic glomerulonephritis, and essential hypertension with superimposed acute toxemia were indistinguishable from each other.

Each, however, could usually be differentiated from uncomplicated hypertension, fluid retention, or normal pregnancy but uncomplicated hypertension and the fluid retention could not be separated by the test alone.

The test was run in 84 patients with excessive weight gain thought to be caused by fluid retention. In 31 who subsequently developed the clinical signs of pre-eclampsia, the values for sodium concentration and total sodium excretion were lower than in those in whom the disturbance in water metabolism remained the only evidence of abnormality during the rest of the pregnancy.

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PROBLEMS ASSOCIATED WITH TOXEMIA IN TWIN PREGNANCIES

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THE increased incidence of toxemia of pregnancy in twin pregnancies has been observed by many authors (Table I). The statistics bearing this fact out, however, have been taken usually from over-all studies of twin pregnancies or from toxemia series. To our knowledge, there has been no attempt made to analyze a series of twin pregnancies with toxemia as to possible methods of induction, mode of management, and complications.

TABLE I. INCIDENCE OF TOXEMIA IN TWIN PREGNANCIES

AUTHOR	TOTAL NO. OF TWIN PREGNANCIES	NO. OF TOXEMIA CASES	INCIDENCE OF TOXEMIA
Potter, Crunden, and Fuller[1, 2] Chicago Lying-in Hospital 1931-1947	538	132	24.5%
Munnell and Taylor[3] 1934-1944	136	24	17.6%
Ross and Philpott[4] McGill University 1947-1951	183	30	17.0%
Kurtz, Keating, and Loftus[5] Margaret Hague 1947-1953	500	141	28.2%

This paper will attempt to study all the twin pregnancies with toxemia that were delivered at the Little Company of Mary Hospital during the years 1950 through 1955. During this time there were 26,004 deliveries with 237 sets of twins. Twin pregnancies of less than seven months' duration were not included in our statistics as the development of toxemia would hardly have been manifest by that time. We did not include cases of essential hypertension unless they were complicated by a superimposed toxemia. Patients with twin pregnancies who developed sudden transient blood pressure elevations post partum following the use of Pitocin or ergot preparations were not considered. The absence of albuminuria and edema and the resumption of normal blood pressure levels within a few hours ruled against the presence of toxemia.

Because the incidence of toxemia is so abnormally high in the primigravid patient in our series, we have made separate studies of the primigravid and the multigravid patients (Tables II, III, and IV).

TABLE II. TOXEMIA IN TWIN PREGNANCIES, THIS SERIES

YEAR	TOTAL NO. OF TWIN PREGNANCIES	TOXEMIA (NO. OF CASES)
1950	31	12
1951	38	12
1952	30	6
1953	31	9
1954	52	13
1955	52	21
Total incidence	234	73 31.2%

TABLE III. PRIMIGRAVIDAS WITH TWIN PREGNANCY AND TOXEMIA, THIS SERIES

YEAR	TOTAL NO. OF TWIN PREGNANCIES	NO. WITH TOXEMIA
1950	11	9
1951	6	4
1952	4	2
1953	4	3
1954	13	9
1955	12	9
Total incidence	50	36 72%

TABLE IV. MULTIGRAVIDAS WITH TWIN PREGNANCY AND TOXEMIA, THIS SERIES

YEAR	TOTAL NO. OF TWIN PREGNANCIES	NO. WITH TOXEMIA
1950	20	3
1951	32	8
1952	26	4
1953	27	6
1954	39	4
1955	40	12
Total incidence	184	37 20.1%

Each case in this series was carefully reviewed in order to evaluate properly the degree of toxemia. Cases of pre-eclampsia were subdivided into mild pre-eclampsia and severe pre-eclampsia, blood pressure being 160/90 or below in the mild cases and above 160/90 in the severe cases. However, factors of degree of edema and albuminuria could change our "severe" to a "mild" classification when the blood pressure was borderline. A patient with a blood pressure, for example, of 164/90 with 1 plus albuminuria and 2 plus edema which subsided after one or two days of therapy was considered to have "mild" pre-eclampsia.

Following this method of classification, our study discloses that of 73 twin pregnancies with toxemia, 40 were classified as mild, while 33 were classified as severe. There were no cases of eclampsia.

TABLE V. INCIDENCE OF ECLAMPSIA IN TWIN PREGNANCIES

AUTHOR	TOTAL NO. OF TWIN PREGNANCIES	NO. CASES OF ECLAMPSIA	PER CENT INCIDENCE
Potter, Crunden, and Fuller[1, 2] Chicago Lying-in Hospital			
1931-1941	281	8	2.9%
1941-1947	257	0	0%
Ross and Philpott[4] McGill University 1947-1951	183	2	1.0%
Kurtz, Keating, and Loftus[5] 1947-1953	500	2	0.4%

The incidence in our series of toxemia in twin pregnancies is much greater in primigravidas (72 per cent) than in multigravidas (20 per cent). This may possibly be due to the fact that the intrauterine and abdominal pressures are not as great in multiparas as in primiparas. The studies of renal and hepatic blood flow indicate that increased intra-abdominal pressure results in decreased blood flow to the kidney with resultant oliguria or anuria, thus contributing greatly to a pre-eclamptic state.

Medical Management

The medical management of toxemia in twin pregnancies was no different in our series of cases than would be the management of toxemia in single pregnancies. There was no standardized pre-eclampsia regimen at our hospital, but the attending doctors adhered quite well to the accepted methods of treatment. Complete bed rest, phenobarbital, intravenous injections of hypertonic glucose, and intramuscular injections of magnesium sulfate were universally employed. Serpasil was used in 7 of the severe cases with marked hypertension and appeared to control the elevated pressure quite well. We had no experience with Veratrum compounds in this series.

Induction of Labor

Because of the high incidence of toxemia in twin pregnancies, and because of its relatively frequent severity, the question often arises as to when and how induction of labor should be performed in these cases. It is recognized by all that surgical induction of labor carries risks to mother and baby. These risks must be carefully evaluated in relation to the risks incurred in doing nothing, or in alternatively performing cesarean section. Blaikley[7] described the case of a primigravida at 32 weeks' gestation with twins in whom severe pre-eclampsia had developed. Induction of labor by rupture of the membranes was elected. Labor did not start for eighty hours and then only after a tube was introduced. She was delivered of twins, but subsequently became febrile. Culture of the lochia showed *Pseudomonas pyocyanea.* She died six weeks later from infective endocarditis due to this organism. Blaikley reported 507 cases of elective induction of labor by rupture of the membranes with a 10.8 per cent morbidity rate. It has been repeatedly observed by many investigators that the induction-delivery interval before 34 weeks can be very long with a correspondingly increased risk of antepartum infection. In twin gestations complicated by severe pre-eclampsia, many inductions must be made before this 34 week stage. Hence, theoretically, the risk should be greater.

Pitocin infusions intravenously have been used successfully in overcoming long latent periods following elective rupture of the membranes. However, in a patient with twin gestation complicated by toxemia, the use of Pitocin is certainly controversial. Many feel that Pitocin is contraindicated in toxemia because of the risk of adding to anoxia already present in the fetus, when the placenta may already be insufficient. With the added factor of a greatly distended uterus from a twin gestation, the additional and more formidable hazard of ruptured uterus must be considered. There have been no convincing reports in the literature as yet as to the safety of intravenous Pitocin drip for induction of labor in the twin pregnancy with toxemia, though Pitocin is reported to have been used successfully eight times in twin pregnancies. However, there have also been maternal deaths reported following the injudicious use of Pitocin for induction of labor in patients with overdistended uteri. It will probably be two or three years before any large series of such cases can be evaluated.

In our series of twin pregnancies with toxemia there were 18 cases in which induction was attempted (Table VI).

In all of our cases of induction the attending doctor tried to treat the toxemia by medical means until the cervix was ripe or near ripe. In 3 cases Pitocin, 1 minim, was given intramuscularly without first rupturing the membranes. In none of these instances did labor result. In 5 out of 6 of our inductions by rupture of the membranes, labor began within 2 to 16 hours. The combination of rupture of the membranes and minim doses of Pitocin

given intramuscularly yielded a 50 per cent success rate. Intravenous Pitocin following rupture of the membranes was used only twice in this series and was effective once. In no instance was cesarean section done. The 7 patients with failed inductions continued to be treated medically and were delivered vaginally 2 to 17 days afterward.

TABLE VI. INDUCTION OF LABOR IN TWIN PREGNANCIES WITH TOXEMIA, THIS SERIES

METHOD OF INDUCTION	NO. OF CASES	EFFECTIVE
Stripping of membranes	1	1
Rupture of membranes	6	5
Intramuscular Pitocin, 1 minim every 15 minutes	3	0
Intravenous Pitocin and rupture of membranes	2	1
Combination of rupture of membranes and intramuscular Pitocin	6	3

Our series of cases of attempted inductions of labor for twin pregnancies with toxemia is admittedly small. It was our impression, however, that Pitocin is not as efficacious an agent for induction in twin pregnancies as it is in single pregnancies. The response of the overly distended uterine musculature appeared sluggish and unpredictable. The possible beneficial effects from increasing the strength of the Pitocin infusion must be weighed against the possible disastrous results that could accrue should the greatly distended uterus rupture.

Fetal Salvage

The over-all fetal mortality rate for our patients with twin pregnancy and toxemia was 4.8 per cent, a figure compatible with most other toxemia series in general.

TABLE VII. FETAL MORTALITY

	NO. OF CASES	FETAL DEATHS	PERCENTAGE
Total births in multigravidas with toxemia	74	1	1.3
Total births in primigravidas with toxemia	72	6	8.4

Our fetal death rate is high in primigravidas with twin pregnancy and toxemia, yet we have no figures available with which to compare these statistics.

The uterine and placental ischemia that occurs in the large distended primigravid uterus with twins might possibly be the mechanism that produces fetal anoxia and subsequently increased fetal loss.

Postpartum Complications

A review of our statistics showing the levels of blood pressure post partum in twin pregnancies discloses an abnormally high increase in many of these cases when the blood pressure is recorded in the recovery ward. Various investigators have studied the effect on blood pressure of drugs used for uterine contraction, and found that intravenous Ergotrate occasionally resulted in acute hypertension which persisted from half an hour to four hours. The hypertensive effect of this drug seems to be even more pronounced on the patient whose uterus is contracting following distention from a twin pregnancy. There were 12 cases in our series in which the excessive rise in

blood pressure post partum resulted in headache, nausea, and visual disturbances, creating all the appearances of impending eclampsia. In retrospect, we now feel that the injudicious use of ergonovine in these patients already toxemic could have been responsible for the fulminating postpartum symptoms. We have now established the policy in our toxemic patients of withholding the drug from those in whom the placenta is expelled without excessive bleeding.

TABLE VIII. POSTPARTUM HEMORRHAGE

	NO. OF PATIENTS	POSTPARTUM HEMORRHAGE	INCIDENCE
Primigravidas	36	10	27.8%
Multigravidas	37	2	5.4%

The abnormally high incidence of postpartum hemorrhage (500 c.c. or more) in the primigravid patient in our series leads us to institute routine typing and cross-matching before delivery. In 6 of these cases the hemorrhage occurred immediately post partum, while in 4 cases it was delayed 2 to 18 hours. Although there were no maternal deaths in this series, 5 of the mothers were in shock from acute blood loss. We have since made a rule in our recovery ward that every patient who delivers twins must be watched closely and checked every five minutes for excessive bleeding or uterine atony. The residents and supervisors are aware that women who deliver twins are especially liable to postpartum hemorrhage. The added factors of primigravidity and toxemia appear to increase greatly this threat of hemorrhage.

Comments

It is apparent from this review of toxemia in twin pregnancies, that the primigravid patient with twins faces a threefold hazard—an inordinately high incidence of toxemia (72 per cent), a greatly increased risk of postpartum hemorrhage (28 per cent), and a higher than average fetal loss (8 per cent). It appears that the primigravid patients with twin pregnancies would be an excellent group for the testing of the multiple theories for prevention of toxemia. For example, Smith and Smith believe that stilbestrol administered daily to the pregnant patient will all but eliminate toxemia. It would be interesting to see what their results would be with a group of primigravid patients with twin gestations.

Many obstetricians routinely x-ray their primigravid patients during the last month of pregnancy. In a considerable number of cases, it is only at this time that the diagnosis of twins is made. It appears to be worth while from the viewpoint of prevention of toxemia to x-ray the primigravid patient early in the last trimester. If twins are diagnosed, the patient could be watched very closely and seen at weekly intervals in an effort to prevent the symptoms and signs of toxemia from developing. Many of the patients in our series had severe toxemia before the diagnosis of twins was made. If these patients had been seen at weekly intervals during the last trimester the toxemia could possibly have been prevented or the degree of toxemia lessened.

With the prevention or control of toxemia in primigravid patients with twin pregnancies, it would be reasonable to expect the high incidence of postpartum hemorrhage to decrease, and possibly the increased fetal loss to be lessened.

Further studies of this problem by other institutions may bear out the conclusion that the over-all high rates of toxemia in twin pregnancies are due largely to the inordinately high incidence of toxemia in the primigravid patient with twins.

Summary and Conclusions

1. In a review of 26,004 deliveries at the Little Company of Mary Hospital from 1950 through 1955, there were 234 sets of twins delivered beyond seven months' gestation. The incidence of toxemia among the mothers was 31.2 per cent.

2. In a further breakdown of statistics it was noted that 72 per cent of all the primigravid patients bearing twins were toxemic. The fetal loss among these primigravid patients was 8.4 per cent. The over-all fetal loss was 4.8 per cent.

3. The problem of induction of labor in the patient with severe toxemia is discussed. The overdistended uterus with a twin pregnancy renders the use of Pitocin controversial and hazardous. The possibility of adding to fetal anoxia from placental and uterine ischemia already present must be considered. Pitocin was not especially effective in the 11 cases in this series in which it was used. Further studies of the use of Pitocin on this particular type patient will be necessary before any conclusions can be drawn.

4. There were 12 cases in which there were fulminating rises in blood pressure immediately post partum, resulting in severe headache and visual disturbances. We have at present established the policy of withholding ergonovine in toxemic patients in whom the placenta is expelled without excessive bleeding.

5. There was an abnormally high incidence of postpartum hemorrhage in the primigravid patients in our series (27.8 per cent). We believe that such patients should be typed and cross-matched before delivery, and blood should be immediately available. These patients must be watched very closely in the recovery ward and any excessive bleeding promptly reported.

6. We recommend that primigravid patients be x-rayed at six months' gestation so that, in the event twins are present, frequent prenatal visits and proper precautionary measures can be taken to guard against the development of severe toxemia.

7. The primigravid patients with twins could serve as an excellent test group for the proving or disproving of some of the current theories on the prevention of toxemia.

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THE ROLE OF THE FIBRINOLYTIC ENZYME SYSTEM IN OBSTETRICAL AFIBRINOGENEMIA*

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TWO theories have been proposed for the production of the afibrinogenemia which is occasionally encountered in obstetrical hemorrhage. One of these suggests that fibrinogen is removed from the blood stream by intravascular deposition as fibrin.[1, 2, 3] The other states that fibrinogen is hydrolyzed by fibrinolysin.[4, 5, 6] It is our opinion that, while the former mechanism may initiate the reaction, it is probably followed by and augmented by hydrolysis due to the activation of the fibrinolytic enzyme system.

This paper presents a detailed study of some of the factors of this enzyme system, including inhibitors, active and potential fibrinogenolysin, fibrinolysin, and hydrolysis products, contained in the plasma of ten women with hemorrhage due to afibrinogenemia. The women included in this report were seen at Sloane Hospital for Women during the period January, 1954, to April, 1955, and represent five cases of premature separation of the placenta and one each of the following diagnosis: placenta previa, elective cesarean section, manual removal of the placenta, dilatation and curettage for incomplete abortion, and a case of ruptured uterus and bladder.

Methods

Fibrinogen Determination.—Results are reported in terms of milligrams of fibrinogen per 100 ml. of plasma using the method of Ratnoff and Menzie[7] which has been found highly satisfactory. It gives readily reproducible quantitative results, and is rapid (45 to 50 minutes) in the hands of an experienced technician. Furthermore, the size of the clot adhering to the ground glass in the first step of the determination gives as reliable a qualitative result (again with an experienced technician) as does any of the so-called rapid methods. In this step, which requires approximately 5 to 10 minutes, fibrinogen levels of below 50 mg. per cent will give no clot or only small shreds when thrombin is added to the diluted plasma; from 50 to 100 mg. a small clot will be obtained; while above 250 mg. per cent a large solid clot will adhere to the ground glass. Levels between 100 and 250 mg. per cent are more difficult to estimate but since the quantitative procedure has already been initiated, an accurate result can be obtained without any loss of time.

Fibrinogenolytic Activity.—This is determined by adding 0.1 ml. plasma to 0.9 ml. phosphate buffer and 1 ml. of 1 per cent fibrinogen solution. This mixture is incubated for 2 hours at 37° C. The reaction is then stopped and pro-

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teins are precipitated by the addition of 3 ml. of 5 per cent trichloracetic acid. After standing one hour the solutions are centrifuged and the optical density of the supernatant fluid is read in a Beckman spectrophotometer at 280 mμ. A blank, prepared by precipitating the proteins immediately after mixing plasma and fibrinogen, is subtracted from this reading. Any increase in optical density is proportional to the tyrosine released from the fibrinogen by a proteolytic enzyme and so may be used as a measure of hydrolysis either directly or the units of fibrinolytic activity may be obtained from a standard curve relating increase in optical density at 280 mμ to units of activity. This standard curve was previously prepared[8] by a method similar to that of Kunitz[9] for trypsin, by hydrolyzing fibrinogen with streptokinase-activated human fibrinolysin as prepared by the method of Lewis and Ferguson.[10] No active fibrinogenolytic enzyme can be demonstrated in normal blood by this method since potent plasma inhibitors neutralize any such activity which may be present. Therefore, even the small activity reported in some cases is significant since only that beyond experimental error appears in the tables.

Streptokinase-Activatable Fibrinogenolysis.—This is determined by adding 0.05 ml. of streptokinase solution to a mixture of plasma and fibrinogen as described above before the 2 hour incubation period. The fibrinogenolytic activity so developed is then determined in a similar manner. This is a measure of the potential fibrinogenolytic activity which is not inhibited by antifibrinolysin found in the plasma. Therefore, an increase in streptokinase-activatable fibrinogenolysin may indicate an increase in profibrinolysin, a decrease in inhibitors, or both. On the other hand, a low value may indicate either that inhibitors have risen or that profibrinolysin has been previously activated and is therefore present in lower concentrations. Because of the multiplicity of factors involved, these results are somewhat difficult to interpret. However, they have been included since their significance may become clearer as more data are accumulated.

Fibrinolytic Activity.—This is measured by a modification of Coon's serial dilution method.[11] In this method plasma is diluted in ratios from 1:2 to 1:64 and then clotted with thrombin. If no fibrinogen is present to form a clot, 0.05 ml. of 1 per cent solution of bovine fibrinogen is added to each tube. The dilutions are allowed to remain at room temperature for 24 hours and then examined for the presence of a clot. Since clot retraction makes difficult evaluation of a 50 per cent lysis (as used by Coon), no lysis is considered to have occurred unless the clot is completely lysed or disintegrates when shaken gently once or twice. Any tube which has lysed completely over a 24 hour period is marked plus and since lysis is most apt to occur in the more dilute tubes a scoring of 3 plus means the three highest dilutions have lysed within 24 hours; 6 plus means all tubes have lysed, etc. Where lysis is known to have occurred in less than 24 hours it is indicated. Normal controls seldom demonstrate any lysis although occasionally a plus-minus will be recorded in the highest dilution. This indicates that a solid clot can be broken up on gentle shaking but that shreds of fibrin remain.

Optical Density of Hydrolysis Products.—Active fibrinogenolysin and fibrinolysin are sometimes difficult to demonstate in vitro. The optical density of the trichloracetic-acid soluble products may give a measure of the hydrolysis that has already occurred intravascularly, however. One-tenth milliliter of plasma is diluted to 2 ml. with buffer and the proteins are precipitated with 3 ml. of 5 per cent trichloracetic acid. The optical density of the supernatant fluid is then determined in a Beckman spectrophotometer at 260, 280, and 295 mμ. Increased optical density indicates that abnormal hydrolysis has occurred, while the absorption at different wave lengths gives some evidence as to the nature

of the hydrolysis products. The absorption peak for purines and pyrimidines is 260 mμ; the peak of maximum absorption for tyrosine is 280 mμ; and the peak for tryptophane, 295 mμ.

Inhibitors of the Fibrinolytic Activity.—A streptokinase-activated fibrinolysin solution is prepared by incubating 1 ml. of profibrinolysin with 0.05 ml. of streptokinase solution and sufficient buffer to make 10 ml., for 10 minutes. A portion of this solution is then diluted 1 to 10. When 0.1 ml. of this dilute preparation is mixed with 1 ml. of 0.05 per cent fibrinogen and the mixture clotted with thrombin, lysis of the clot occurs in approximately 12 minutes. Addition of small quantities (0.05-0.2 ml.) of dilute plasma (1 to 10) to the mixture before clotting causes an inhibition with normal blood samples and the lysis time is increased.

If the concentration of fibrinolysin uninhibited is expressed

$$C_u = \frac{1}{T} \times 100$$

while the concentration of fibrinolysin with inhibitor added is

$$C_i = \frac{1}{T_i} \times 100$$

then the inhibition in units produced by 1 ml. of plasma may be defined as

$$\text{I.U.} = \frac{C_u - C_i}{\text{ml. plasma}} .$$

The inhibitor units so measured at different concentrations of plasma do not remain constant but normally increase with dilution. Therefore inhibition was determined at several levels of plasma concentration. The figures reported are those obtained at the highest dilution or at a concentration of 0.005 ml. plasma in a standard fibrin clot.

Materials

Dried potassium oxalate was used to prevent coagulation.

Profibrinolysis for calibration curves was prepared by the method of Lewis and Ferguson[10] using recalcified human plasma obtained from overage blood from the blood bank.

Phosphate buffer at pH 7.4 in 0.90 per cent sodium chloride was used. In most cases 0.05 M phosphate was employed. However, the profibrinolysin was dissolved and stored in 0.01 M buffer.

*Bovine fibrinogen powder** was dissolved to a concentration of 2 per cent in phosphate buffer. Since this powder contains 42 to 48 per cent clottable protein this solution will contain approximately 0.9 per cent fibrinogen. Some lot numbers of fibrinogen powder have proved unsatisfactory for use in these determinations, probably because of a high concentration of profibrinolysin.

Commercial thrombin† (bovine origin) containing 1,000 N.I.H. units per milliliter was used.

Streptokinase‡ was dissolved in 0.05 M phosphate to give a solution containing 10,000 units per milliliter.

Case Histories

CASE 1.—H. L. was a 35-year-old white, private patient, para i, gravida iii, with an estimated date of confinement of May 21, 1954. At 8:00 A.M. on April 8, she was awakened

*Armour Laboratories.
†Parke, Davis & Company.
‡Varidase from Lederle Laboratories Division, American Cyanamid Company.

with generalized severe abdominal pain but no uterine bleeding. When she was admitted at 11:00 A.M. with a tense, diffusely tender uterus, no fetal heart sounds were audible. Blood drawn at this time formed an apparently adequate clot in 4½ minutes.

At 1:30 P.M., bright red bleeding occurred. Membranes were ruptured and a Pitocin infusion was started. Blood for fibrinogen determination was drawn at this time. At 2:58 P.M. there was a normal spontaneous delivery of a stillborn 1,200 gram male infant. The placenta, showing gross signs of recent hemorrhage, was delivered almost immediately followed by a large clot. The fundus contracted well. At this time the plasma fibrinogen was reported at 7 mg., per cent, and the clot formed at 11 A.M. was observed to be completely lysed.

During repair of the episiotomy each puncture wound from the needle bled freely. The blood pressure was 130/90. By 3:30 P.M. hemorrhage was profuse. One gram of fibrinogen* was given at 3:40 with no rise in plasma fibrinogen level. Two additional grams were administered 15 minutes later. The blood pressure had fallen to 95/60.

At 4:30, the fibrinogen was 28 mg. per cent but the bleeding had begun to decrease. Ten mg. of Hykinone was given at 5 P.M. By 6:00 P.M. the blood pressure had risen to 122/80 and bleeding was very scant. At 7:40, the fibrinogen level was 166 mg. per cent and no further difficulties were encountered.

In August, 1955, this patient delivered a normal living child. Fibrinogen levels were followed carefully during this pregnancy but no complications ensued (Table I).

TABLE I. FIBRINOLYSIN STUDIES ON H. L.

TIME	FIBRINOGEN (MG. %)	FIBRINOGENOLYSIN		INHIBITORS (UNITS)	OPTICAL DENSITY		
		ACTIVE	STREPTOKINASE ACTIVATABLE		260	280	295
8:00 A.M.	Onset of abdominal pain						
1:30 P.M.	7	0.55	4.8	0	156	162	93
2:58	Delivery						
3:40	3 Gm. fibrinogen, I.V.						
4:30	28	0	3.3	350	97	149	
7:30	166	0	3.5	540	98	160	
Next day	154	0	4.1	700	102	166	

Within 5 or 6 hours of the first onset of symptoms of abruptio placentae, this patient had developed a very acute afibrinogenemia in spite of the fact that blood drawn 2 hours earlier had shown a normal clotting time. However, the clot had lysed completely within the 2 hours. An active fibrinogenolysin could be detected in the plasma and the inhibitor units were zero, at the dilution determined. A high optical density at all wave lengths suggests that hydrolysis of fibrinogen had been taking place intravenously.

In spite of the low fibrinogen level, no alarming hemorrhage occurred until after delivery, when clinical symptoms typical of afibrinogenemia developed. After intravenous administration of 3 Gm. of fibrinogen, bleeding gradually subsided. The first response shown in the plasma was reflected in the inhibitor level but the fibrinogen also rose gradually until it had reached nearly normal levels after 4 hours.

CASE 2.—L. R. was a 34-year-old Negro woman, para 0, gravida iii, with an obstetrical history of two spontaneous early abortions and an estimated date of confinement of April, 1955. At 6:45 P.M. on Jan. 1, 1955, the patient developed nausea and subsequent vomiting associated with faintness and weakness. This was followed by the onset of sharp, constant abdominal pain and vaginal bleeding. When first seen, one hour after the onset of symptoms, the patient was bleeding actively and experiencing infrequent uterine contractions. The

*Parenogen, Cutter Laboratories.

blood pressure was 108/70; pulse 80. No fetal heart sounds were audible nor could fetal outlines be made out. Blood, drawn for cross-matching, failed to clot in one hour and subsequent determination showed a complete absence of fibrinogen.

At 8:00 P.M. the blood pressure had fallen to 84/58. One thousand milliliters of blood and 1 Gm. of fibrinogen were given. At 8:45 the membranes were ruptured with the release of bright red blood and blood-tinged amniotic fluid. At 9:00 P.M. with the blood pressure at 140/90, an additional gram of fibrinogen was given because of continued bleeding.

At 10:15, the fibrinogen level was 98 mg. per cent. Another 500 ml. of blood was started and a third gram of fibrinogen was given at 11:15. The vital signs remained stable and bleeding diminished.

At 1:48 A.M. there was the spontaneous delivery of a stillborn premature male infant, followed by the loss of approximately 600 ml. of blood in large clots. The placenta was almost 75 per cent separated. The fibrinogen level, half an hour postpartum, was 122 mg. per cent. At 2:30, because of a slight persistent ooze of bright red blood when the uterus was atonic, a Pitocin infusion was commenced and 1,000 ml. of whole blood was added. By 9:30 A.M. the lochia was apparently normal.

On January 4, the fibrinogen level was 264 mg. per cent. Deep thrombophlebitis in the right lower extremity manifested itself on the seventh postpartum day. Anticoagulant therapy for 2 weeks resulted in the complete disappearance of symptoms of phlebitis (Table II).

TABLE II. FIBRINOLYSIN STUDIES ON L.R.

TIME	FIBRINOGEN (MG. %)	FIBRINOGENOLYSIN		FIBRINOLYSIN (COON'S)	INHIBITORS (UNITS)	OPTICAL DENSITY		
		ACTIVE	STREPTOKINASE ACTIVATABLE			260	280	295
6:45 P.M. Onset of abdominal pain								
7:00	0	0.3	13.3	++++	0	89	117	83
8-9	2 Gm. fibrinogen, I.V.							
10:15	98	0	11.0	–	60	54	94	67
11:15	1 Gm. fibrinogen, I.V.							
1:48 A.M. Delivery								
2:15	122	0	11.2	–	200	43	88	62
3 days	264	0	4.4	–	540	69	107	75

This is the only patient of the group in whom severe hemorrhage due to afibrinogenemia was manifested but subsequently controlled before delivery. Prompt treatment with fibrinogen raised the blood content to levels which permitted clotting; vital signs were stabilized by replacement of blood loss; bleeding had decreased within 2 hours after the initiation of therapy; spontaneous delivery was accomplished without undue loss of blood.

While active fibrinogenolysin and fibrinolysin could be demonstrated in the blood drawn on admission, none was present in subsequent samples drawn after the administration of fibrinogen. The inhibitor level, which was zero at the time of admission, increased with the fibrinogen level.

CASE 3.—A. S. was a 36-year-old white para i, gravida ii, with an estimated date of confinement of September 15, 1954. At 9:00 A.M. on July 22, there was a sudden onset of low midline uterine pain, associated with distinct uterine enlargement, but no contractions or external bleeding. The patient was admitted at 12:30 P.M. with the uterus tense and hard, and undergoing superimposed contractions. No fetal heart sounds could be heard. The membranes were ruptured artificially, releasing clear amniotic fluid but no blood. Following this, the uterus decreased in size. Fetal heart sounds were now faintly audible.

At 1:00 P.M. blood was drawn for a fibrinogen determination, which was later reported as 47 mg. per cent. At 1:50 there was a sudden gush of approximately 500 ml. of bright red

blood per vaginam. A 1,800 gram infant, delivered by cesarean section, was resuscitated with difficulty and died within 12 hours. The placenta was completely separated and 600 ml. of fresh and clotted blood was found in the uterine cavity. The uterus presented a typical Couvelaire appearance. A pint of whole blood was administered intravenously during closure, because of active bleeding.

At 2:30 the blood pressure was 70/50. An additional 500 ml. of blood, under pressure, and 1 Gm. of fibrinogen brought the blood pressure to 120/60 by 2:50. One more gram of fibrinogen and 500 ml. of blood were given. From 3 to 5 P.M. moderate bleeding continued per vaginam but vital signs remained normal. Pitocin and Ergotrate were given intramuscularly.

At 5:00 P.M., the fibrinogen level was 122 mg. per cent; by 5:50 bleeding was diminishing. A Pitocin infusion was started to maintain uterine tone. By 8:00 P.M., the lochia was normal. The next day fibrinogen was 236 mg. per cent and the remainder of the postpartum course was uneventful (Table III).

TABLE III. FIBRINOLYSIN STUDIES ON A. S.

TIME	FIBRINOGEN (MG. %)	FIBRINOGENOLYSIN		OPTICAL DENSITY		
		ACTIVE	STREPTOKINASE ACTIVATABLE	260	280	295
9:00 A.M.	Onset of abdominal pain					
1:00 P.M.	47	0.35	11.8	67	65	27
1:55	Cesarean section					
2:30	2 Gm. fibrinogen, I.V.					
3:30	"	0.35	10.3	84	60	29
5:00	122	0.30	8.3	34	44	26
Next day	236	0	3.9	26	48	30

Since this is the only case of severe hemorrhage with abruptio placentae in which cesarean section was done, it is interesting that a Couvelaire uterus was found.

CASE 4.—P. H. was a 33-year-old para 0, gravida iv, Negro woman, with an estimated date of confinement of March 22, 1954. Her previous obstetrical history included two spontaneous abortions and a primary cesarean section for partial premature separation of the placenta. The infant was stillborn and the patient's postoperative course was characterized by two episodes of pulmonary infarction, secondary to deep pelvic phlebitis requiring anticoagulation therapy for six weeks. During the present pregnancy under close antepartum supervision the patient showed no symptoms of toxemia, nor any exacerbation of her preexisting chronic hypertensive cardiovascular disease.

In the early morning of March 9, the patient noticed the uterus becoming hard. By 6:00 A.M. she began to have constant lower abdominal pain and vomited once. She was admitted at 7:40 with blood pressure 110/70, pulse 96. The uterus was term sized, distended, firm and not relaxing, and moderately tender. Fetal heart sounds were inaudible. There was no external bleeding. The blood drawn for cross-matching clotted solidly in three minutes.

At 8:15, a classical cesarean section was performed to deliver a term-sized stillborn female infant. There was complete separation of the placenta with approximately 1,500 ml. of fresh and clotted blood within the uterine cavity. Dextran, 500 ml., and 1,000 ml. of whole blood were administered. Immediately postoperatively the fibrinogen level was 78 mg. per cent but there was no undue bleeding.

The following day the fibrinogen level had risen to 238 mg. per cent and anticoagulation therapy was begun. This was continued for 17 days when a short episode of bleeding occurred. At this time, the prothrombin time was 39 seconds and the fibrinogen level 142 mg. per cent. Bleeding subsided within three days and the patient was discharged April 4 (Table IV).

TABLE IV. FIBRINOLYSIN STUDIES ON P. H.

TIME	FIBRINOGEN (MG. %)	FIBRINOGENOLYSIN		INHIBITORS (UNITS)	OPTICAL DENSITY		
		ACTIVE	STREPTOKINASE ACTIVATABLE		260	280	295
6:00 A.M.	Onset of abdominal pain						
8:15	Cesarean section						
9:00	78	0.2	5.6	0	24	104	70
Next day	238	0	5.9	280	69	119	81
March 30	142	0.4	4.8	300		102	

This case is presented as an example of a premature separation with a somewhat lowered fibrinogen level which did not require fibrinogen. Since no active bleeding was occurring, fibrinogen was withheld and the level gradually returned to normal. Some time later another episode of bleeding occurred during which the level was depressed.

CASE 5.—B. S. was a 19-year-old Negro, para 0, gravida i, whose antepartum course was characterized by a 26 pound gain in weight but no other symptoms of toxemia. On March 17, 1954, at 11 A.M., labor began spontaneously, followed in thirty minutes by the sudden onset of vaginal bleeding. The patient was admitted to the hospital at 11:45, bleeding actively and complaining of constant abdominal pain with superimposed contractions. The blood pressure was 140/100, pulse 96, and albumin 3 plus. Fetal heart sounds were 60 so the patient was taken immediately to the operating room. At this time, the fibrinogen was 159 mg. per cent. The baby was delivered spontaneously at 12:08 P.M., but survived only 15 minutes. The placenta was delivered immediately, completely separated.

Slight bleeding was noted during the episiotomy repair which increased to a steady ooze of bright red blood with a fall in blood pressure to 98/64 at 12:50 P.M. A pint of whole blood was started. At 1:55 a proximal extension of the episiotomy was discovered and repaired.

At 3 P.M., the fibrinogen level was 77 mg. per cent. Additional whole blood, Ergotrate, and Hykinone were given and a Pitocin infusion was started at 3:50. Bleeding began to diminish and by 5 P.M. the lochia was apparently normal. At this time the fibrinogen level was 133 mg. per cent. At midnight, the fibrinogen level had fallen again to 112 mg. per cent, perhaps due to hemodilution, but no excessive bleeding was noted.

At 7:30 the following morning the fibrinogen was 156 mg. per cent. The patient continued to improve and was discharged in good health (Table V).

TABLE V. FIBRINOLYSIN STUDIES ON B. S.

TIME	FIBRINOGEN (MG.%)	FIBRINOGENOLYSIN		INHIBITORS (UNITS)	OPTICAL DENSITY		
		ACTIVE	STREPTOKINASE ACTIVATABLE		260	280	295
11:00 A.M.	Labor started						
11:30	Active bleeding started						
12:00 noon	159	0	3.6	270		103	
12:08 P.M.	Delivery						
3:00	77	0	3.9	210	70	103	76
5:00	133	0	4.0	350		98	
12:00 midnight	112	0	3.5	420		109	
7:30 A.M.	156	0	3.2	480		117	
Second day	222	0	3.7	495		116	

This is another example of a patient who developed a low fibrinogen level but recovered spontaneously without intravenous administration of fibrinogen. Prompt delivery may have prevented development of a severe hemorrhagic difficulty.

CASE 6.—H. B. was a 35-year-old Negro, para iv, gravida vi, with an estimated date of confinement of April 6, 1955. She was admitted for observation on March 20 because of scant painless bleeding but was discharged after 48 hours. On March 28 at 2:30 A.M., after 2 hours of active labor a normal spontaneous delivery occurred. Considerable fresh blood and clots followed the delivery of the baby; the placenta was expelled rapidly, accompanied by moderately active bleeding. The blood pressure became unobtainable within an hour. Massage of the fundus caused the passage of a large quantity of fresh blood and clots. A Pitocin infusion and 1,000 ml. of Dextran were started. At 4:00 A.M., on examination, the active bleeding was found to be coming from an apparently intact cervix. The uterine cavity was packed with gauze.

From 4:25 to 4:55, 1,500 ml. of whole blood was given under pressure into a cut-down in the left arm. Oozing from the cut-down incision was the first indication of a clotting deficiency. A blood sample, drawn at this time, was found to have no fibrinogen. Four grams of fibrinogen and 1,000 ml. of blood failed to control bleeding.

On manual exploration of the uterus, a huge rent was found in the lower segment. The patient was now in severe shock with no peripherally detectable blood pressure and pulse 140, weak and thready. She was taken immediately to the operating room where blood was noted to be coming from the urethra. A Foley catheter was inserted into the bladder but no urine was obtained.

On operation, the tear was found in the right anterolateral surface of the lower uterine segment extending into the floor of the bladder. There was a massive collection of blood, air, and urine in the right broad ligament, and retroperitoneal space. A total hysterectomy with right salpingo-oophorectomy was performed with a repair of the bladder laceration. Four pints of whole blood were administered under pressure during the operation. At 8:45, the patient was sent to the recovery room with blood pressure 70/0, pulse 144, weak and thready. At 9:00 urine formation began and the blood pressure began to rise.

At 11 A.M., the hematocrit was 35.6 per cent and fibrinogen 152 mg. per cent. A pint of whole blood and 2 Gm. of fibrinogen were given, followed by 500 ml. of fresh blood. By 1:00 P.M., the blood pressure had risen to normotensive levels and remained there.

At 6:00 P.M. the fibrinogen level had risen to 292 mg. per cent. The urine output in the first 24 hours postoperatively was 750 ml. There was no further bleeding. On March 31, the fibrinogen was 386 mg. per cent. The convalescence was uneventful (Table VI).

TABLE VI. FIBRINOLYSIN STUDIES ON H. B.

TIME	FIBRINOGEN (MG.%)	FIBRINOGENOLYSIN		FIBRINOLYSIN (COON'S)	INHIBITORS (UNITS)	OPTICAL DENSITY		
		ACTIVE	STREPTOKINASE ACTIVATABLE			260	280	295
12:45 A.M.	Admitted in early active labor							
2:30	Normal spontaneous delivery							
4:45	0	0.2	7.6	++++++	110	87	87	58
6:30	Total hysterectomy							
11:00	152	0	3.4	–	180	82	125	83
6:00 P.M.	292	0	3.9	–	290	79	104	69
3 days	386	0	3.4	–		96	113	81

This patient exhibited the most severe hemorrhage of the group and is the only one who required more than 3 Gm. of fibrinogen therapeutically. This case is particularly interesting in view of the fact that the bladder was ruptured and urine,[12] which has been reported a most potent activator of the fibrinolytic enzyme system, was found in the peritoneal cavity. While mechanical causes could easily account for the extensive bleeding, other factors must be responsible for the afibrinogenemia. As in other cases presented here, the inhibitor level was depressed in the first sample studied but increased after administration of fibrinogen.

CASE 7.—L. B. was a 22-year-old Puerto Rican, para i, gravida ii, with an estimated date of confinement of Aug. 25, 1954, and an uneventful prenatal course. The patient was admitted on August 4 for a rest prior to delivery by elective secondary cesarean section.

On August 20, a 2,459 gram female infant, living and well, was delivered by low flap cesarean section. The placenta and membranes were removed manually and intact. During closure the uterus relaxed frequently in spite of repeated administration of Ergotrate, and Pitocin given intravenously. Active bleeding occurred during closure and 500 ml. of blood was started. By the end of the operation there was a fall in blood pressure to 70/40 and an acceleration of pulse to 140. The patient had an estimated blood loss of 1,000 ml. in the immediate postoperative period. A pint of Dextran, 1,000 ml. of whole blood, and a Pitocin infusion were given.

At 11 A.M., the first step of the quantitative fibrinogen determination showed a low level by deficient clot formation so 2 Gm. of fibrinogen was given immediately. When the determination was completed, the level was shown to be 54 mg. per cent. By noon there was a subsidence of active bleeding and vital signs were stabilized.

By 3:00 P.M. the fibrinogen was 120 mg. per cent. The remainder of the postpartum course was uneventful. When the clips were removed a small incisional hematoma and multiple ecchymosis about the clip marks were disclosed (Table VII).

TABLE VII. FIBRINOLYSIN STUDIES ON L. B.

TIME	FIBRINOGEN (MG.%)	FIBRINOGENOLYSIN		FIBRINOLYSIN (COON'S)	OPTICAL DENSITY		
		ACTIVE	STREPTOKINASE ACTIVATABLE		260	280	295
9:30 A.M.	Cesarean section						
10:30	54	0.2	3.1	+++	61	91	62
11:00	2 Gm. fibrinogen, I.V.						
11:30	170	0	2.75	++	52	82	56
3:00 P.M.	126	0	2.65	++	40	76	50

No explanation can be offered as to the cause of the afibrinogenemia displayed by this patient. The secondary section was performed electively and no difficulty was encountered until the sudden onset of hemorrhage during closure. Leary[13] has reported a similar case. The patient responded rapidly to the administration of fibrinogen with an increase in the fibrinogen level and subsidence of the slight evidence of lytic enzyme activity which had been obtained previously.

CASE 8.—A. M. was a 30-year-old white private patient, para 0, gravida i, with an estimated date of confinement of June 12, 1954. Her antepartum course had been uneventful except for two episodes of vaginal bleeding during the seventh month. On the morning of June 21 at 3:35 A.M., she was admitted to the hospital, having passed a small amount of bright red blood. The membranes were intact and there were no contractions. At 6 A.M. placentography suggested a possible placenta previa. The bleeding increased somewhat and at 10:30 A.M. a sterile vaginal examination with a double set-up showed a central placenta previa. An immediate classical cesarean section was performed to deliver a 2,840 gram infant girl in good condition. Active bleeding occurred following the removal of the placenta and caused a fall in blood pressure to 90/50 and a pulse of 120 but the bleeding subsided shortly. The patient received 1,500 ml. of whole blood. The blood pressure remained low and vaginal bleeding increased.

At 1:15 P.M. the bleeding had become profuse and the blood pressure was 70/50, pulse 132. At 2 P.M. the fibrinogen level was found to be 28 mg. per cent. The uterus was packed; 500 ml. of blood under pressure and 1 Gm. of fibrinogen were administered, with a resulting rise in blood pressure to 110/70. Another pint of blood was started.

At 3 P.M. the fibrinogen was 46 mg. per cent. By 4:15, the blood pressure was 118/78, pulse 80, and fibrinogen 84 mg. per cent. Although no further bleeding was evident through the packing, an additional gram of fibrinogen was given to assure adequate hemostasis. The next day the fibrinogen level was 364 mg. per cent (Table VIII).

TABLE VIII. FIBRINOLYSIN STUDIES ON A. M.

TIME	FIBRINOGEN (MG.%)	FIBRINOGENOLYSIN		FIBRINOLYSIN (COON'S)	OPTICAL DENSITY		
		ACTIVE	STREPTOKINASE ACTIVATABLE		260	280	295
10:30 A.M.	Cesarean section						
2:00 P.M.	28	0.2	11.2	+++++	89	102	62
2:30	1 Gm. fibrinogen, I.V.						
3:00	46	0	10.0	+	69	102	63
5:00	84						
5:30	1 Gm. fibrinogen						
Next day	364						

CASE 9.—M. T. was a 22-year-old para i, gravida iii, Puerto Rican, whose last menstrual period was Dec. 17, 1954. At midnight on March 26, she was admitted with a diagnosis of inevitable early abortion. Pitocin infusion was started and the products of conception were delivered spontaneously and apparently intact at 1:30 A.M. Scant-to-moderate bright red bleeding continued throughout the morning and at 2:15 P.M. a routine dilatation and curettage was performed. This was productive of abundant decidual tissue and multiple small placental fragments.

A slight but persistent ooze of bright red blood continued to issue through the cervix; the uterus was packed. Within less than 5 minutes, the packing was saturated. Curettage was repeated, removing several minute placental fragments. The uterus was repacked tightly with gauze. At this time the bleeding time was 5 minutes; the venous clotting time 10 minutes; and the fibrinogen was 191 mg. per cent.

Again the packing was completely saturated within 5 minutes so the uterus was gently explored. A small placental fragment was removed. Within 5 to 10 minutes the vagina was completely filled with blood which did not clot. The uterus was repacked twice but the packing was again expelled within 10 minutes. From 4:15 to 5:00 the uterus was held in acute anteflexion bimanually. Bleeding during this period continued, although somewhat decreased in quantity, and did not clot.

At 4:45, blood for a second fibrinogen determination was drawn. While the determination was being made, a sample was drawn for clot observation. The specimen clotted normally within 3 to 5 minutes but within 10 minutes had lysed almost completely to a water consistency. At 5.30, the fibrinogen level of the blood drawn 45 minutes earlier was reported as 170 mg. per cent. On the basis of a decreasing fibrinogen level and an active fibrinolysin, 2 Gm. of fibrinogen was administered.

At 7:30 the fibrinogen was 243 mg. per cent and there was no further bleeding. During the whole procedure the patient had received 1,500 ml. of whole blood, and 1,000 ml. of Dextran, in addition to fibrinogen and oxytocics (Table IX).

TABLE IX. FIBRINOLYSIN STUDIES ON M. T.

TIME	FIBRINOGEN (MG.%)	FIBRINOGENOLYSIN		FIBRINOLYSIN (COON'S)	INHIBITORS (UNITS)	OPTICAL DENSITY		
		ACTIVE	STREPTOKINASE ACTIVATABLE			260	280	295
2:15 P.M.	Curettage							
3:00	191	0	3.5	++++	260	66	66	47
4:45	170	0	4.3	+++	340	79	72	54
5:30	2 Gm. fibrinogen, I.V.							
7:30	243	0	3.4	+	410	93	90	68

CASE 10.—J. R., a 34-year-old Negro, para i, gravida iii, was admitted to the hospital Jan. 13, 1955, with spontaneously ruptured membranes. On January 18 at 6:21 A.M., after five hours' labor, a male infant was delivered spontaneously. This infant showed signs of respiratory distress and difficulty of unknown origin and died within a few hours. The placenta failed to separate after 42 minutes and was removed manually, apparently intact. The fundus did not maintain tone well and heavy uterine bleeding started at 7:50 A.M. and continued despite Ergotrate, Pitocin infusion, and continued massage.

Blood drawn at 9:30 had a fibrinogen level of 89 mg. per cent. Two pints of whole blood was given and at 10:30 on re-examination a small cervical laceration was noted and repaired. No membranes or placental cotyledons were found in the uterus. It was noted that blood drawn for cross-matching at 7:50 either had never clotted or had lysed in the interval. One gram of fibrinogen was given intravenously at 11:20.

At 12:15 P.M. the fibrinogen level was 170 mg. per cent. A third pint of blood was started. Bleeding decreased and vital signs were maintained satisfactorily. By 6 P.M. the lochia was apparently normal. Two days later the fibrinogen was 564 mg. per cent. No further bleeding was encountered (Table X).

TABLE X. FIBRINOLYSIN STUDIES ON J. R.

TIME	FIBRINOGEN (MG.%)	FIBRINOGENOLYSIN		FIBRINOLYSIN (COON'S)	INHIBITORS (UNITS)	OPTICAL DENSITY		
		ACTIVE	STREPTOKINASE ACTIVATABLE			260	280	295
6:21 A.M.	Delivery							
7:00	Placenta delivered manually							
9:30	89	0.2	3.5	++++++	240	61	84	59
11:20	1 Gm. fibrinogen, I.V.							
12:15 P.M.	170	0.2	4.3	+	280	47	84	61
2 days	564							

Results

Fibrinogen Levels.—Of the 10 cases reported here, 6 had fibrinogen levels below 25 mg. per cent, 3 between 55 and 89 mg. per cent, and one had a minimum level of 170 mg. per cent. All of the patients with levels below 55 mg. per cent received fibrinogen intravenously in quantities of 2 or 3 Gm. (except H. B., 6 Gm.) per person in order to control postpartum hemorrhage. Two patients with levels at approximately 75 mg. per cent did not require fibrinogen therapy but two others with higher levels (89 and 170) were given fibrinogen because the alarming hemorrhage did not appear to be responding to the more conservative treatment of whole blood and oxytocics.

In the cases of abruptio placentae, the time from the onset of symptoms to the time at which the lowest fibrinogen levels were obtained varied from one to 6 hours, with an average of about 4 hours. The first determination was the lowest in most cases, so that the time interval required to produce afibrinogenemia cannot be estimated with any accuracy. In 2 cases (H. L. and B. S.), however, the fibrinogen levels obtained shortly after the first symptoms of abruptio were observed are known to be higher than the lowest levels reported. This time lag is more suggestive of an enzymatic hydrolysis of fibrinogen than it is of the alternate theory of fibrin deposition.

After fibrinogen therapy was instituted, bleeding usually showed a marked decrease within 30 to 60 minutes, and changed to apparently normal lochia within 3 hours. By this time, fibrinogen levels had risen to 120 mg. per cent or higher.

Fibrinolytic Activities.—Small but significant evidence of an active fibrinogenolytic or proteolytic enzyme was demonstrable in 8 of the 10 cases presented. These include all of the more severe cases of hemorrhage. In addition, the streptokinase-activatable fibrinogenolysin showed large increases in 5 of the 10 patients and small increases in 2 others. This increase may be due to increased profibrinolysin in the blood stream or to decreased inhibitors. The latter interpretation seems more reasonable, in these instances, since inhibitor levels, when they were studied, were found to be considerably lowered in most cases. After fibrinogen therapy was initiated, as the fibrinogen levels rose, inhibitors and streptokinase-activatable fibrinogenolysin levels returned to normal.

Considerable fibrinolytic activity was also found in all cases where serially diluted plasma clots were observed for lysis. This activity also disappeared rapidly after fibrinogen had been given intravenously.

The optical densities of trichloracetic acid-soluble products, which may be an indication of hydrolysis occurring intravascularly, showed a great deal of variation. However, 6 of the 10 cases showed optical densities above 100 at 280 mμ while all but one were above the averages obtained with patients who had uncomplicated deliveries.

Comments

Schneider[1] has proposed a possible mechanism for the initiation of the fibrinogen depletion as well as methods by which extracts from decidual and placental tissues may get back into the maternal blood stream. Since these tissues contain thromboplastin, it is conceivable that the clotting mechanism may be activated intravascularly and fibrinogen may be deposited as fibrin emboli.

Since such fibrin emboli are seldom found in any appreciable quantity (i.e., enough to account for 8 to 12 Gm. of circulating fibrinogen), however, such a deposition of fibrin must be followed by an activation of the fibrinolytic enzyme system. By lysing the clots formed, this enzyme would prevent the occlusion of the blood vessels by the emboli. Furthermore, the enzyme could contribute to the fibrinogen depletion by hydrolysis of the fibrinogen itself. Since all of these tissues contain an activator of the fibrinolytic enzyme system as well as thromboplastin,[8] entrance of such extracts into the maternal blood stream, as suggested by Schneider, might also lead to the activation of the profibrinolysin present in normal blood.

In addition, it has been demonstrated that the myometrium of the pregnant uterus contains potent activators of this enzyme system. Therefore, the flow of blood through an enlarged uterus may tend either to initiate or to increase the activation of the proteolytic enzymes in the blood stream. Margulis[14] has shown that the presence of such an enzyme can be demonstrated even during normal delivery. This possible mechanism is further supported by the fact that Couvelaire changes of the uterus are frequently noted in cases of afibrinogenemia in which cesarean sections have been performed for abruptio placentae.

Although fibrinolysin or plasmin is the name commonly given to this enzyme, in all probability it consists of a number of different enzymes. Therefore it may be that different precursors are activated by substances such as chloroform, streptokinase, and tissue extracts or that a different activity is produced

from the one proenzyme by each of these activators. As shown in a previous paper[8] the fibrinogenolytic activity is stimulated by tissue extracts to a greater extent than is the fibrinolytic activity. An equal variety of inhibitors probably are to be found in normal blood.

The presence of a fibrinolytic enzyme has been reported by some investigators[4, 5, 6, 15, 16] and suggested by the data of others.[17] The enzymes involved in this system are exceedingly labile, however, and can be quickly destroyed under normal in vitro conditions at room temperature or at 37° C. Thus Lewis[18] was best able to show activation of the system by incubation at refrigerator temperature for a period of one to two weeks, because of the rapid inactivation which occurred at higher temperatures. Therefore, even small evidences of hydrolysis or lysis, in vitro, may have a definite clinical significance and may indicate that a much greater reaction is taking place in vivo.

Scott and associates[19] have suggested that the presence of an active proteolytic enzyme in the blood stream may be responsible both for the hemorrhage found occasionally in surgical and obstetrical patients, and for the shock accompanying it, even in cases where fibrinogen levels are normal. These authors suggest giving the albumin fraction of blood as a source of antifibrinolysin. Although no conclusions as to cause or effect can be made from the present work, it is of interest that, as bleeding subsided, vital signs stabilized, and fibrinogen levels rose, the enzyme activities also returned to normal levels, and the inhibitor levels increased. It may be that the fibrinogen fraction of blood aids in the restoration of normal blood conditions by introducing inhibitors of the fibrinolytic enzyme system as well as by providing a substrate for clot formation.

No cases of homologous serum jaundice have been reported in any of this group although 2 patients received the same lot number as that given to 2 patients with surgical hypofibrinogenemia who contracted the disease within six months of receiving fibrinogen.

Summary

1. Case histories of ten patients with obstetrical afibrinogenemia are presented. Serially collected blood samples were studied for fibrinogen levels and for the various factors of the fibrinolytic enzyme system. Small but significant levels of fibrinolytic and/or fibrinogenolytic activity were found in most of these patients.

2. It is suggested that this proteolytic activity may be at least partially responsible for the low levels of fibrinogen found in these patients.

3. Intravenous administration of fibrinogen resulted in an increase in fibrinogen levels and in a control of abnormal bleeding. Inhibitor levels and enzyme activities showed a concomitant return to normal.

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BLOOD COAGULATION DURING NORMAL PREGNANCY, LABOR, AND THE PUERPERIUM

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THE classic theory of blood coagulation was described in 1904 by Morawitz.[1] This theory, which included all the coagulation factors known at that time, consisted of two phases. The first was the formation of thrombin from prothrombin which occurred in the presence of thromboplastin and calcium. At that time it was thought that thromboplastin came from the platelets. The second phase was the change of fibrinogen to fibrin in the presence of thrombin. No essential changes were made in this theory until recently, when renewed interest in coagulation followed Quick's[2] description of the one-stage prothrombin time. A number of new factors were then described, and several additions were included in the coagulation mechanism.

Stefanini's[3] recent review of coagulation listed three essential groups of factors: (1) those which arise from the platelets, (2) those which occur in plasma, and (3) those which are found in serum. The platelet factors are four in number: (1) platelet thromboplastic factor which activates thromboplastinogen, (2) platelet factor I which induces prothrombin to thrombin conversion, (3) platelet factor II which accelerates the conversion of fibrinogen into fibrin, and (4) platelet factor III which opposes the activity of heparin. The factors that occur in plasma are divided into two groups: (1) those which are used in coagulation, namely, (a) thromboplastinogen, (b) prothrombin, (c) calcium, (d) plasma Ac-globulin, (e) proconvertin, and (f) fibrinogen; and (2) those which oppose coagulation, namely, (a) antithromboplastin, (b) antithrombin, (c) heparin cofactor, and (d) profibrinolysin. The factors that occur in the serum are (1) all the factors found in plasma, except fibrinogen, in concentrations directly related to their utilization in coagulation, (2) serum Ac-globulin, (3) convertin, (4) thrombin, and (5) metathrombin.

The present theory of coagulation utilizes these components and is initiated by the destruction of platelets with the release of their factors. When thromboplastin is formed, a minimal amount of prothrombin is converted to thrombin. Thrombin is needed for the activation of the labile accelerator, Ac-globulin. Since this part of the mechanism is autocatalytic, the Ac-globulin converts an excess of prothrombin to thrombin. In the presence of this excess, fibrinogen

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is changed to fibrin and coagulation occurs. The excess thrombin is adsorbed onto the surface of the fibrin. This effectively prevents defibrination by removing this excess.

Based on this theory, Bell[4] proposed a series of tests for coagulation effectiveness which together he called a "coagulogram." This consists of the following: (1) platelet count by the Rees-Ecker[5] technique, (2) oil clot retraction time by the Hirschboeck[6] technique, (3) the prothrombin consumption test of Quick,[7] (4) one-stage prothrombin time of Quick, (5) Ac-globulin determination of Stefanini,[8] (6) fibrin determination by a variation of Ratnoff's[9] technique, (7) coagulation time by the Lee-White[10] method, and (8) protamine titration for circulating anticoagulants by Allen's[11] technique. The first three tests show the platelet count and effectiveness. The next three are for the plasma factors. Coagulation time is a nonspecific test for all these factors. The last test is a titration for the heparinoid anticoagulants.

In a recent review[12] we found no studies carried out during late pregnancy, labor, and the puerperium which included serial determinations for all these factors. There are, however, notable studies of a single factor. The need of normal values for the various coagulation factors during late pregnancy, labor, and the early puerperium thus seems obvious.

Material

Twenty normal pregnant patients who were in the thirty-fourth week of gestation were selected and followed from this time through delivery and the early part of the puerperium. Twelve were nulliparous and eight were primiparous. A complete coagulogram was done on each patient at each of the following times: thirty-fourth week, thirty-sixth week, thirty-seventh week, thirty-eighth week, thirty-ninth week, in early labor, 5 minutes after delivery of the placenta, and at the end of 24 and 72 hours of the puerperium.

Methods

All determinations were carried out in duplicate except the protamine titration for circulating anticoagulants.

The platelets were counted by the Rees-Ecker technique. A change of plus or minus 20,000 platelets is considered significant by this method. Normal values are 200,000 to 300,000 per c. mm.

Oil clot retraction time was determined by placing a drop of venous blood on the surface of castor oil in a 75 mm. by 8 mm. glass test tube, with the blood hanging from the oil-air interphase, forming a smooth spherical shape. The end point was recorded by the appearance of an eccentric "pimple" of serum on the side of the sphere. The normal values range between 25 and 45 minutes with an average of 36 minutes.

The serum prothrombin determination was carried out one hour after coagulation occurred and represents that amount not utilized and remaining in the serum. The test compares the results obtained by doing a one-stage prothrombin determination on the patient's plasma and serum. Bovine fibrinogen was used as a substrate for the serum. The difference in clotting times for the serum and plasma represents the difference in prothrombin present. When 14.6 seconds is considered to represent 100 per cent prothrombin in the test on plasma, normal serum will take an additional 20 seconds or more; thus indicating 70 to 80 per cent prothrombin utilization as shown by Langdell.[13]

In the one-stage prothrombin determination 14.6 seconds for the mixture to clot is considered to represent 100 per cent prothrombin concentration in our laboratory.

The test for accelerator globulin was carried out by adding 0.01 c.c. of the plasma being tested to 0.09 c.c. of normal plasma in which the accelerator globulin had deteriorated. With the addition of thromboplastin and calcium to this mixture in a Lee-White tube, the clotting time was determined. If Ac-globulin were added in the plasma being tested, this mixture would clot in a period of time in excess of 14.6 seconds and in our laboratory this time was 20 seconds when the plasma being tested contained a normal amount of Ac-globulin. This time is in excess of the normal because the Ac-globulin is added in such a small amount. If there is a deficit of accelerator globulin in the plasma being tested, there will be a further prolongation of this time in excess of 20 seconds.

Fibrin determinations were carried out by a variation of the technique described by Ratnoff in which the fibrin was allowed to clot on a serrated glass rod, then retrieved, blotted thoroughly with filter paper, and carefully washed with normal saline. Following hydrolysis with sodium hydroxide, the phenol reagent was added and an aliquot tested for its tyrosine content in the Klett photocolorimeter.

The test for heparinoid activity was carried out by adding a known amount of heparin to the blood (400 mcg. per cubic centimeter of whole blood) and titrating this against a known quantity of protamine sulfate. In general, 100 to 140 mcg. of protamine was required to neutralize the 200 mcg. of heparin added to the blood (using 0.5 c.c. aliquots). Any increase in heparinoid activity was demonstrated by the need for more protamine sulfate to induce coagulation. This test was designed to detect small increases in heparinoid activity, since the chemical test for heparin is cumbersome and does not detect small increases of this anticoagulant.

Coagulation time was determined by using Lee-White tubes and taking the second of two tubes as representing the significant coagulation time. The normal range for this method was 3 to 10 minutes.

Results

The data were subjected to statistical analysis; the mean values and two standard deviations appear in Table I. The variation of the mean values was not significant when they were analyzed.

The platelets and their function tests are summarized in Fig. 1. The platelets ranged from 230,000 to 250,000 between the thirty-fourth and thirty-eighth weeks. There was a decrease to 220,000 at the thirty-ninth week and to 210,000 in early labor. An abrupt rise to 250,000 occurred in late labor and continued into the puerperium when the mean value reached 270,000. The oil clot retraction time gradually shortened in the antepartum period to reach 42 minutes in early labor. It dropped to 36 minutes after delivery of the placenta and remained near this level during the puerperium. The consumption of prothrombin, as reflected in the serum prothrombin time, remained about the same during the antepartum period at approximately 50 seconds. In early labor the serum prothrombin time shortened to 45 seconds as less prothrombin was consumed. It remained at reduced levels until the puerperium, when the consumption of prothrombin rapidly increased and the serum prothrombin time increased to 54 seconds.

The plasma factors are summarized in Fig. 2. The prothrombin, by the one-stage method, was 76 per cent until the thirty-eighth week. There was a slight decrease to 70 per cent at the thirty-ninth week and it remained near

TABLE I. COAGULATION FACTORS AND HEMATOCRIT

	PLATELETS (THOUSANDS PER C.MM.)	OIL CLOT RETRACTION (MINUTES)	PROTHROMBIN		AC-GLOBULIN (%)	FIBRIN (MG. %)	PROTAMINE TITRATION (MCG.)	COAGULATION TIME (MINUTES)	HEMATOCRIT (MM.)
			SERUM (SECONDS)	PLASMA (%)					
Late Pregnancy.—									
34 weeks' gestation	230 ± 116.0	48 ± 32.0	50 ± 37.7	75 ± 37.2	85 ± 28.2	480 ± 117.0	160 ± 64.0	10 ± 6.3	33 ± 5.4
36 weeks' gestation	250 ± 142.0	44 ± 24.5	47 ± 33.6	76 ± 23.2	86 ± 14.1	440 ± 86.0	160 ± 66.0	10 ± 5.5	34 ± 6.9
37 weeks' gestation	240 ± 144.0	42 ± 28.5	49 ± 27.0	76 ± 24.1	89 ± 18.9	450 ± 99.0	140 ± 67.0	9 ± 4.1	34 ± 6.6
38 weeks' gestation	250 ± 119.0	37 ± 18.3	50 ± 39.6	73 ± 29.9	88 ± 20.1	450 ± 72.0	160 ± 46.0	10 ± 5.7	34 ± 6.6
39 weeks' gestation	220 ± 94.0	44 ± 31.9	50 ± 32.3	70 ± 25.6	86 ± 14.9	430 ± 91.0	140 ± 87.0	11 ± 7.2	35 ± 7.8
During Labor.—									
Early labor	210 ± 102.0	42 ± 23.7	45 ± 28.4	72 ± 24.7	91 ± 14.7	430 ± 107.0	140 ± 69.0	10 ± 6.3	34 ± 9.1
After placenta	250 ± 157.0	36 ± 26.5	46 ± 27.1	70 ± 26.8	94 ± 13.6	400 ± 126.0	140 ± 69.0	9 ± 7.0	36 ± 12.2
Early Puerperium. —									
24 hours	250 ± 107.0	36 ± 27.4	54 ± 27.8	75 ± 28.0	93 ± 18.7	490 ± 96.0	140 ± 77.0	8 ± 3.0	36 ± 13.2
72 hours	270 ± 130.0	35 ± 17.0	53 ± 32.7	74 ± 26.8	92 ± 15.5	520 ± 114.0	150 ± 82.0	9 ± 6.7	32 ± 11.0

this level until the puerperium, when it returned to the predelivery level. The accelerator globulin fluctuated during the antepartum period, attaining a level of 86 per cent at the thirty-ninth week. There was an increase up to 94 per cent in labor which was noted after the placenta was delivered. A slight decrease to 92 per cent occurred at 72 hours in the puerperium. Fibrin levels

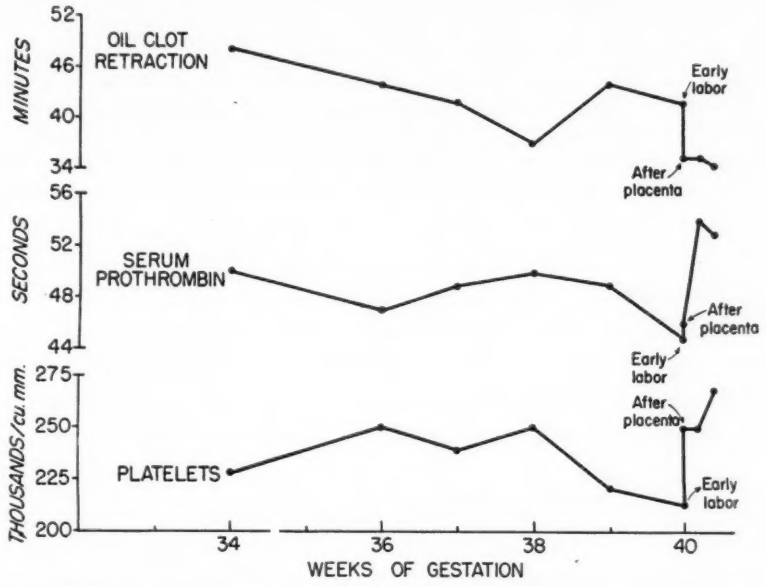


Fig. 1.—Platelet counts, oil clot retraction, and prothrombin utilization in 20 normal pregnant patients during late pregnancy and delivery. As the prothrombin time of serum becomes shorter, more prothrombin is present and less is consumed in the process of clotting.

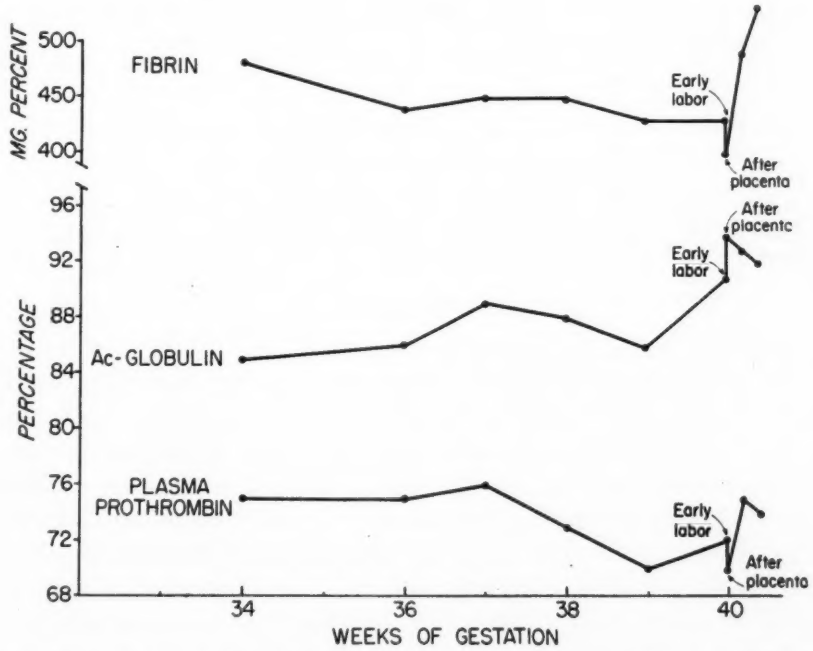


Fig. 2.—Fibrinogen as fibrin, Ac-globulin, and plasma prothrombin in 20 normal pregnant patients during late pregnancy and delivery.

ranged from 450 to 480 mg. per cent in the antepartum period. There was a trend downward at the thirty-ninth week which continued into labor and was most marked after delivery of the placenta, when the mean value was 400 mg. per cent. The fibrin increased rapidly in the puerperium and was 520 mg. per cent at the 72 hour period.

The coagulation time, protamine titration, and hematocrit determinations are summarized in Fig. 3. The protamine titration for heparinoid substance showed some fluctuation during the antepartum period with stabilization at the thirty-ninth week. The titration showed no change in these substances during labor and the early puerperium. There was a slight increase noted at the 72 hour period of the puerperium. The coagulation time varied around 10 minutes in the antepartum period. There was slight shortening of the coagulation time during labor, which continued into the puerperium, when it was 8 minutes.

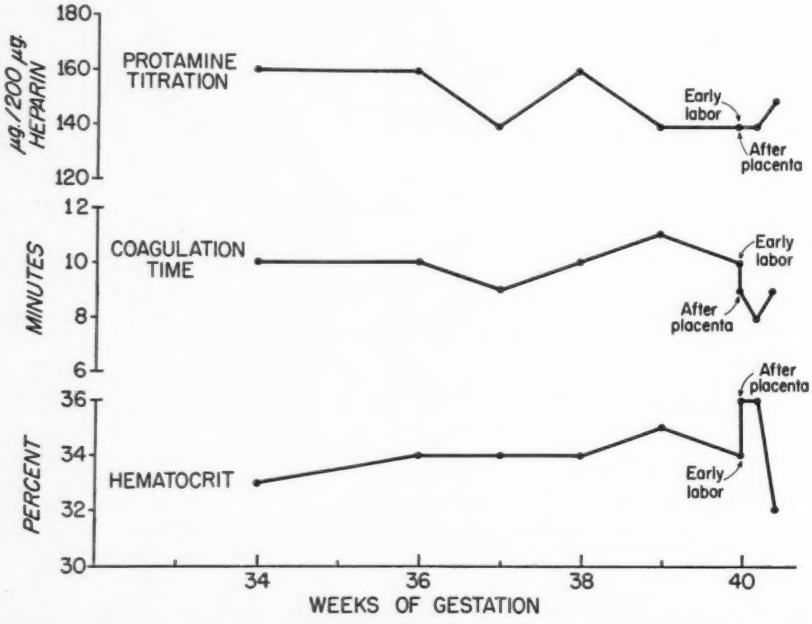


Fig. 3.—Coagulation time, hematocrit, and protamine titration for heparinoid anticoagulants in 20 normal pregnant patients during late pregnancy and delivery. The quantity of protamine ordinarily required to neutralize the added heparin is 140 mcg. Any increases in the protamine requirement are considered due to a circulating "heparinoid type" substance.

Comment

In blood coagulation the significance of a change in one of the factors is difficult to determine because of the several variables that enter into the testing. These are: (1) sensitivity and reproducibility, e.g., the errors of the method, (2) those due to individual difference, and (3) those which may result from changes in the plasma volume. We have tried to limit the errors introduced by methods by having the determinations done in duplicate by the same individual.

Individual difference as a variable was probably significant before the thirty-ninth week, for during this period the grouping was probably due to this. During this time, the platelet counts of 5 patients were consistently under 150,000. Four had prothrombin levels above 80 per cent and 4 had levels below 60 per cent. There were 4 patients who had a fibrin level above 500 mg. per

cent and one whose fibrin level remained below 300 mg. per cent. The fluctuations that occurred after the thirty-ninth week probably resulted from an increased utilization in the body's protective mechanisms or changes in stimulation of production. During the time immediately prior to labor, 7 patients had an increase in platelets and 13 had a decrease. Twelve had longer clot retraction, 7 had shortened clot retraction, and one specimen was lost. Six patients had more prothrombin consumption and 14 had less. Six had an increase in fibrin, 2 had no change, and 12 had a decrease.

During labor individual difference did not seem to enter into the changes that occurred, for the increase in platelets was reflected in a proportionate increase of prothrombin consumption and faster clot retraction with a majority of the patients exhibiting these changes. Fourteen of the patients had an increase in platelets, 12 had faster clot retraction, and 15 had more prothrombin consumed. These changes clearly support the thesis that prothrombin consumption and clot retraction vary directly with the number and quality of the circulating platelets. The other factor that appeared to be affected by the process of labor was fibrin, with 5 patients having an increase, 2 having no change, and 12 a decrease.

The changes that occurred in the puerperium probably resulted from a reparative stimulus, for the trend was toward increased ability of the blood to clot. During this period 15 patients had a continued increase in platelets with 11 showing faster clot retraction and 13, an increase of prothrombin consumption. The fibrin, increased in 14 patients, remained the same in one and decreased in 5.

The effect upon clotting factors of changes in plasma volume may be significant. With the decrease in plasma volume that occurs in the last trimester,[14] there is a divergence of the albumin and globulin concentration, the latter increasing. Both the prothrombin and fibrinogen have an electrophoretic mobility pattern that occurs in the globulin range. Their increase may thus reflect plasma concentration if one assumes that albumin is selectively decreased. Crawford[15] and Caton[16] concluded that hemoconcentration occurred in normal patients during the last seven antepartum days, especially the last two. The changes that occurred during this time were toward a decrease in platelets, fibrinogen, prothrombin, and Ac-globulin and thus are not explainable in this way. Pastore[17] stated that the changes in blood volume were usually slight during the labor unless labor was prolonged and associated with dehydration. The changes that occurred during labor would thus be the result of stimulation in production or utilization in the body's protective mechanisms if the changes in plasma volume noted by Lowenstein[18] were sufficiently evanescent. In the immediate puerperium there is an apparent sudden decrease in the plasma volume which approaches the predelivery value during the ensuing 24 hours.[16] The postpartum diuresis begins at this time and the plasma volume gradually returns to the prepregnancy level. These changes in the puerperium may have

contributed to the increase of the clotting factors, for associated with this loss of plasma volume there was a definite increase in the coagulation factors. The hematocrit determinations that we carried out would support this thesis.

Of the variables that entered into this study, only those having to do with the methods were definitely controlled. Individual variation and changes in plasma volume may have contributed to the results. We expect that the changes noted in the platelets and fibrin would have been significant in a larger series.

Summary and Conclusions

1. The coagulation mechanism was studied in 20 patients and the results presented for late pregnancy, labor, and the puerperium.

2. A decrease in fibrin and platelets occurred near term, suggesting a utilization of these factors during the early phase of labor.

3. It appears that fibrinogen is utilized for hemostasis during labor as it is during a surgical procedure.

4. A definite stimulus occurs for platelet production during labor.

5. The increase of platelets, prothrombin, and fibrinogen that occurred during the puerperium is further confirmatory evidence that these factors may contribute to the embolic phenomena which are common at this time.

6. There are normal fluctuations in these factors during parturition which in no instance, with our present knowledge, would have caused any major bleeding difficulties.

7. This study of the coagulation trends occurring in normal pregnancy is presented with the hope that further investigation of coagulation in both the normal and abnormal obstetrical patient will be stimulated.

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THE MATERNAL AND PERINATAL MORTALITY OF CESAREAN SECTION

A Report of 2,693 Operations Performed in Brooklyn During 1954

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CRITICAL examination of cesarean section experience has long been an important duty of the obstetrician. His attention has been directed particularly to the lessening of maternal risk, while fetal and neonatal mortality have received somewhat scant notice, are often not mentioned, or are so reported that statistical comparisons are not possible.

In the final analysis, of course, warrant for cesarean section must rest upon maternal results, yet as maternal risk grows less with expanding indications, interest in perinatal mortality must quicken. All the mortality associated with the operation should be studied, not only maternal but fetal and neonatal. Since definition and report of stillbirth vary in practice, this component of perinatal mortality may make rates noncomparable. In the case of cesarean section, however, this should not be true.

Results obtained by a great many operators of varying degrees of skill and experience, in a large number of hospitals of various types, should offer a more worth-while opportunity for study than the series of a few very capable obstetricians or the product of a highly organized clinic. And, too, review of a large number of operations performed during the same year should reflect current risk better than statistics accumulated over a long period of time. Outline of the vast cesarean section panorama of New York City should help to chart the issues. Here are more than 8,000,000 people, of every race and language and every station in life. The rate of cesarean section per 1,000 live births has risen from 19.9 in 1937 to 50.2 in 1954. Rates for the last twelve years are shown in Table I.

In common statistical practice cesarean section rates refer to the number of live births, not the actual number of operations. No correction is made for multiple births, nor are cesarean sections associated with fetal death taken into account. To discover the true incidence of cesarean section every operation must be included, and for calculations of the perinatal mortality rate, every stillborn fetus, as in this table.

In Brooklyn, a borough of the City of New York, are 2,734,000 people, about one-third of the population of this immense city; non-whites are estimated at 250,000. In 1953,[1] when all the neonatal deaths which occurred in Brooklyn were studied, it was found that obstetric complications played an important part and it appeared that attention to cesarean section should get sizable results in the reduction of general perinatal mortality.

TABLE I. INCIDENCE OF CESAREAN SECTION IN NEW YORK CITY FROM 1943 TO 1954

YEAR	CESAREAN SECTIONS		LIVE BIRTHS		FETAL DEATHS	
	NUMBER	RATE*	NUMBER	RATE†	NUMBER	RATE‡
1943	4,117	29.7	4,001	29.7	116	29.7
1944	4,195	33.2	4,090	33.3	105	28.5
1945	4,795	36.2	4,654	36.1	141	37.6
1946	5,753	36.6	5,583	36.6	170	38.5
1947	6,729	38.3	6,536	38.2	193	42.1
1948	6,873	42.4	6,689	42.3	184	43.8
1949	7,093	44.1	6,901	44.0	192	48.6
1950	7,404	46.4	7,253	46.5	151	41.2
1951	7,821	47.0	7,632	46.9	189	49.8
1952	8,206	48.8	8,007	48.8	199	51.9
1953	8,186	49.6	8,015	49.6	171	48.0
1954	8,408	50.1	8,233	50.2	175	46.3

*Per 1,000 live births plus fetal deaths at 20 and more weeks.
†Per 1,000 live births.
‡Per 1,000 fetal deaths at 20 and more weeks.

Material for Study

The confidential data on every certificate of birth by cesarean section which occurred in Brooklyn during 1954 (with matching certificates for every maternal and neonatal death) were furnished by the Bureau of Records and Statistics of the Department of Health of the City of New York. Additional information was obtained from hospitals. Operations reported as cesarean section which, on investigation, proved to be anterior hysterotomy early in pregnancy were excluded, and several cases of hysterectomy for rupture of the uterus in the course of pelvic delivery or afterward, reported as cesarean hysterectomy, were also weeded out. No case was included in which the fetus was outside the uterus. It is certain that no cesarean section was lost.

From Jan. 1, 1954, to Dec. 31, 1954, cesarean section was performed on 2,693 women; 2,361 were white and 332 were non-white; 2,130 women were private patients, and 563 women were delivered in service wards. The operations were performed in 37 hospitals.

It is worth remembering that in Brooklyn from 1937 to 1950, cesarean section had been a constant factor in about 20 per cent of all puerperal deaths.[2] This span embraces a remarkable period in obstetrics, in which the risk of death has decreased considerably. In 1937 Watson[3] said that in most well-conducted clinics the mortality of cesarean section ranged from 2 to 5 per cent, and that the rate for the entire country was probably 10 or 15 per cent. He estimated the risk of abdominal delivery to be ten times that of vaginal delivery, when both were carried out under the best auspices. We can hardly realize the enormous change.

In 1954 the total number of live births in Brooklyn was 56,106 and the number of fetal deaths reported as at 20 weeks and over was 1,204. There were 23 maternal deaths; 3 of these deaths and 90 of a total 940 neonatal deaths were associated with cesarean section.

Type of Operation.—The classical operation was performed in 110 cases, the lower segment operation in 1,711 cases, and an extraperitoneal procedure in 12 cases. Hysterectomy was performed in 16 cases under the following circumstances: previous cesarean section, 5; placenta previa, 2; abruptio placentae, 2; diabetes, 2; fibromyomas, 2; and toxemia, 3. In 860 cases the type of operation is not known. The parity in 2,693 cases is shown in Table II.

TABLE II. PARITY IN 2,693 CASES OF CESAREAN SECTION, BROOKLYN, 1954

PARITY	NO. OF CASES
First baby	1,122
Second baby	1,017
Third baby	334
Fourth baby	123
More than four	97
Total	2,693

Multiple Pregnancy.—Twin pregnancy was found in 20 cases. The indications for operation were: previous cesarean section, 8 cases; placenta previa, 4 cases; toxemia, 3 cases, 1 associated with diabetes; and others (5 cases).

One small fetus, long dead, was found at operation for disproportion at term, its twin being delivered alive. There were 6 neonatal deaths. After operation for placenta previa at 24 weeks, twins, each weighing less than 1,000 grams, lived about two hours; and non-white twins, each about 1,500 grams in weight though calculated to be close to term, died shortly after operation elected because of previous cesarean section. Twins of a diabetic mother, one weighing 1,924 grams and the other 934 grams, survived. A set of twins lived after rupture of a previous cesarean section scar.

Indications.—The indications for operation were, on the whole very clearly stated; often more than one reason was given. To resolve this problem, indications, with related fetal and neonatal deaths, are arbitrarily separated in Table III.

TABLE III. INDICATIONS FOR CESAREAN SECTION

INDICATION	NO. OF CASES	PERINATAL MORTALITY		TOTAL
		FETAL	NEONATAL	
Antepartum hemorrhage:				
Cause unknown	5		1	1
Abruptio placentae	79	24	11	35
Placenta previa	184	4	16	20
Diabetes mellitus	35		1	1
Disproportion	559	4	7	11
Dystocia	263	3	5	8
Elderly primipara	59		1	1
Fetal indication	114	1	2	3
Pelvic tumors	23		1	1
Previous cesarean section	1,042	2	30	32
Pelvic operation	45	2	3	5
Toxemia	116	3	10	13
Miscellaneous	64	1	2	3
Unknown	105			
Total	2,693	44	90	134

Dystocia includes all indications reported as prolonged labor (123 cases), midpelvic arrest (20 cases), occiput posterior (13 cases), nonengagement (7 cases), cervical dystocia (10 cases), and abnormal presentation (90 cases). In the group of elderly primiparas 23 women were 40 years of age or more, and one was 47 years old. The fetal indication includes fetal distress and prolapse of the cord (105 cases) and previous stillbirths (9 cases). Pelvic tumors were largely myomas, and previous pelvic operations were chiefly myomectomy. In the miscellaneous group 31 cases were reported simply as elective. Only one case of rupture of the marginal sinus of the placenta was reported.

Previous cesarean section deserves especial mention since it accounted for 38.7 per cent of all the cesarean sections; in this group were toxemia (3 cases),

placenta previa (4 cases), and diabetes (4 cases). For 31 women this was the third abdominal delivery; and 3 women had had three and 2 had already had four cesarean sections.

Rupture of a Cesarean Section Scar.—In the 3 cases in which the scar of a previous cesarean section was found to have ruptured, all the infants survived. There was one maternal death. Brief data of these cases are of interest:

CASE 1.—A white woman 39 years of age who had had 3 cesarean sections previously was operated upon in the thirty-eighth week of her fourth pregnancy. A lower segment scar was found to be partially ruptured. The placenta was in the lower segment. The membranes were intact. Resuture of the area of rupture and tubal ligation were performed. Twins in the weight group from 2,500 to 3,500 grams survived.

CASE 2.—In a white woman 31 years old, rupture of the scar of her third cesarean section occurred in the thirty-seventh week of her fourth pregnancy. Resuture and tubal ligation followed delivery of a 2,000 gram infant, who survived.

CASE 3.—Cesarean section in the thirty-eighth week was planned for a white woman 28 years of age, whose first baby had been born by cesarean section. In the thirty-seventh week she was admitted to the hospital after several hours of labor at home. At operation, an upper segment scar was found to be ruptured, with considerable blood in the peritoneal cavity; the amniotic sac was intact. The placenta and a live fetus weighing 4,247 grams were removed through the wide-open scar which was then resutured. Death in a few hours was due to hemorrhage and shock.

Maternal Mortality.—There were 3 maternal deaths in 2,693 operations, or 0.01 per cent, all in the group who had previous cesarean sections. With the possible exception of the case in which death followed rupture of a cesarean section scar, it is difficult to see how death might have been prevented. The essential data of the other 2 cases are of interest:

CASE 1.—A 27-year-old Negro had been delivered once by cesarean section for preeclampsia. About a year later she was admitted to the hospital for pyelonephritis in the eighteenth week of her second pregnancy. At this time and upon two subsequent admissions urine culture was consistently positive for *Aerobacter aerogenes.* After a septic course, during which repeated sensitivity tests showed the organism to be resistant to all antibiotics, right nephrostomy was performed without clinical improvement. In a final effort, classical cesarean section was performed in the thirty-fourth week of pregnancy; a 3,100 gram infant survived. Dehiscence of the wound occurred on the sixth day and the wound was reclosed under local anesthesia. Death occurred in the fourteenth postoperative day after a convulsion. At autopsy a perinephritic abscess was found.

CASE 2.—Under spinal anesthesia lower segment cesarean section was performed at term upon a 34-year-old obese white woman who had been delivered previously by cesarean section; the abdominal scar was excised. An infant who weighed 3,170 grams survived. On the eighth day the patient was unable to open her mouth. Rigidity of the neck, opisthotonos, and convulsions followed. Death occurred on the eighth postoperative day. Smears from the abdominal wound in anaerobic media showed a few gram-positive bacilli with terminal spores. All attempts at subculture were unsuccessful. Autopsy was essentially negative except for a large soft spleen. Cultures from the uterine cavity, brain, and spinal cord were negative. The clinical diagnosis of tetanus was concurred in by many consultants including one from the Department of Health.

Perinatal Mortality

For 2,714 births by cesarean section, in terms of 1,000 births, the fetal mortality rate was 16.2 (44 stillbirths), the neonatal mortality rate 33.2 (90 deaths), and the perinatal mortality rate 49.4.

Following good statistical practice,[4] birth weight was used as the measure of the maturity level at birth. Though the gestation age stated may have been reasonably correct, it was not used, since its shortcomings are well known. Birth weights were derived from vital records for all babies born by cesarean section whether alive or dead and for all infants in this operative group who died within 28 days after birth. When birth weights were reported in pounds and ounces, gram groupings with class intervals of 500 grams were used to tabulate the data in Table IV.

The concentration of cesarean section births was in the group between 2,500 and 4,000 grams. Of the total number of children born, 10.6 per cent weighed 2,500 grams or less. Only a few births fell in the upper weight interval of 4,500 grams or more.

Perinatal mortality refers to death of fetuses before birth and of infants in the first few days of life. After cesarean section, death of the infant, when it occurs, usually takes place early in the neonatal period. All but one of the 90 neonatal deaths occurred within the first five days of life. Mortality was closely related to birth weight. More than half of the neonatal deaths were in the weight intervals below 2,501 grams.

TABLE IV. PERINATAL MORTALITY BY BIRTH WEIGHT OF 2,713 INFANTS BORN BY CESAREAN SECTION

WEIGHT IN GRAMS	TOTAL	FETAL DEATHS	NEONATAL DEATHS	TOTAL DEATHS
Less than 1,000	17	1	8	9
1,001-1,500	21		8	8
1,501-2,000	64	7	19	26
2,001-2,500	187	3	21	24
2,501-3,000	635	9	14	23
3,001-3,500	933	2	12	14
3,501-4,000	623	3	5	8
4,001-4,500	154	1	1	2
4,501-5,000	51			
Over 5,000	11	1	2	3
Unknown	17	17		17
Total	2,713*	44	90	134

*Includes twins and fetal deaths.

It is not necessary to comment in detail on all these data. The low perinatal mortality associated with operations performed primarily in the interest of the fetus, as in the elderly primipara, for hypoxia due to interference with the cord, and for diabetes is notable. There were 2 neonatal deaths in 39 operations upon diabetic patients, one of whom had already had three stillbirths; in 4 of these operations the indication was previous cesarean section; twins weighing 1,000 grams and 1,800 grams survived, though severe pre-eclampsia supervened in the thirty-sixth week. In 44 fetal deaths, 11 fetuses were non-white; and there were 12 non-white in the neonatal group.

Though anesthesia was found to be the principal cause in 20 per cent of all the maternal deaths associated with cesarean section in Brooklyn from 1937 to 1950,[2] its role in perinatal mortality cannot be readily shown. It appears to be an important factor, yet, since precise data could not be obtained for all cesarean sections, no assessment of the risk of anesthesia is made here.

More than half of the fetal deaths followed abruptio placentae. There were 2 cases of hydrocephalus, one associated with placenta previa. There were 3 cases of protracted labor, and 7 patients were in early labor; in each case the fetus weighed 2,500 grams or more, one 5,748 grams. In 2 cases of fetal death the indication was previous cesarean section; in one section performed in the thirty-eighth week the fetus was known to be dead of erythroblastosis; in the other at elective operation in the thirty-eighth week, a fetus weighing 4,000 grams was born dead.

In the group of neonatal deaths severe defects of the central nervous system were reported in 5 cases and erythroblastosis in 5 cases. Complete autopsy reports were not quickly available. Death was commonly attributed to anoxia and asphyxia. Hyaline membrane was reported in 3 cases. It may be said that nearly all the deaths were due to failure of the fetal respiratory system to adapt itself to extrauterine life. This has been pointed out by Morrison,[5] who said that autopsy fails to reveal the cause of death in a large percentage of cases. In other words, it shows how death occurred but not necessarily why.

Antepartum hemorrhage was the principal cause of perinatal death, accounting for 42 per cent of the total. Previous cesarean section, aside from any other indication with which it was coupled, was related to another 24 per cent of the perinatal deaths. The largest number of neonatal deaths were associated with previous cesarean section. Weight groups in these two important complications are shown in Table V.

TABLE V. MAJOR CLINICAL CAUSES OF PERINATAL DEATHS BY BIRTH WEIGHT OF INFANTS (87 CASES)

WEIGHT IN GRAMS	TOTAL NO.	PLACENTA PREVIA		ABRUPTIO PLACENTAE		PREVIOUS SECTION	
		FETAL	NEONATAL	FETAL	NEONATAL	FETAL	NEONATAL
Less than 1,000	17		4	1	2		
1,001-1,500	21		2	1	1		2
1,501-2,000	64	1	7	4			9
2,001-2,500	187		3	4	4		9
2,501-3,000	635	1		7	2		5
3,001-3,500	933			1	2		4
3,501-4,000	623	1				1	1
4,001-4,500	154						
4,501-5,000	51						
Over 5,000	11						
Unknown	17	1		6		1	
Total	2,713	4	16	24	11	2	30

Maternal Risk

We are told[6] that the attempt of obstetricians to limit the incidence of cesarean section to 6 per cent or less has resulted in a persistent high mortality for the fetus and an avoidable maternal trauma; that a hospital regulation requiring consultation prior to cesarean section is discriminatory and favors procrastination; that the operation may be performed by a general practitioner, since it is not a serious one; that cesarean section is preferable to any obstetric operation other than the simplest type of low forceps; and that it is not beyond the realm of possibility that the day will come when all women will be delivered by cesarean section. Another[7] hopes that the rate will increase until anything but the simple operative vaginal deliveries will become completely obsolete.

The central theme of this study, however, is not to question the immediate benefits of cesarean section, but rather its consequences. Many facets of the problem are commonly pushed into the background. With the spotlight on low maternal mortality, the possibility of nonfatal complications appears to fade into nothingness.

D'Esopo's[8] study of 1,000 operations performed at Sloane Hospital might well serve as a model of reporting. There was no maternal death, yet there was some form of puerperal infection in 107 cases. The list of other postpartum complications he calls "impressive": wound disruption, 2; wound infection, 29; wound of bladder, 1; atelectasis, 3; intestinal obstruction, 2; thromboembolic disease, 24; and many more but lesser ones.

Hemorrhage got special mention. There was need for transfusion of 500 c.c. to 2,000 c.c. of blood in 378 cases. Shock occurred in 27 cases. In general the need for blood replacement was considerably greater than in other laparotomy. Postpartum hemorrhage was severe in two patients, one of whom had to have hysterectomy. Blood loss can surely be reckoned on, but not the amount.

It is hardly necessary to establish the assumption that, once cesarean section has been performed, no matter how afebrile the puerperium, subsequent pregnancy may result in rupture of the scar of operation in the uterus. Many factors play a part in this accident, but the principal cause must be imperfect healing. Separation of the uterine wound may occur more quietly than dehiscence of the abdominal incision, even in the puerperium. Before operation, however, this possibility is not given a moment's thought. Whether operation had been performed in the upper or the lower segment of the uterus makes very little difference, except perhaps in the time of frank rupture.

The present frequency of rupture of the cesarean section scar is not known. A few recent reports should be of interest. Eames[9] collecting 79 cases found it to be 2.6 per cent. Schmitz and Gajewski[10] reported 3.6 per cent. Diddle[11] in six hospitals in Tennessee reported 5.6 per cent, and a 5.04 per cent figure comes from the Philippines.[12] King[13] in 435 secondary cesarean sections performed in New Orleans in 1951-1952 encountered but 2 ruptures but found 20 very thin scars; 16 of these women were not in labor.

Eastman[14] thinks that the incidence of rupture is less than 2 per cent, while Colvin[15] estimated it at 3 to 4 per cent, yet neither took into account dehiscence of the scar which has largely gone unrecorded and unreported. Lane and Reid's[16] recent report of 3.3 per cent dehiscence observed in 426 lower segment scars is of prime importance. Their conclusion that the upper segment scar is more likely to rupture during pregnancy than in labor, while the reverse is true of the scar in the lower segment, if supported, should make an enormous change in our thinking. Since the senior author is rightly regarded as one of our most thoughtful obstetricians, his views are significant.

The number of ruptured scars occurring in the obstetric experience of any group will not give us the information we want, however, for many of

their cesarean section patients never have another pregnancy or cannot be found. Only a large number of abdominal deliveries with the subsequent history of every patient over a considerable period of time may be the basis of calculation. Holland[17] in his classic study of 1920, first pointed out that this was elementary. He found the incidence of rupture to be 4 per cent, but all the ruptures he studied, with but one exception, had occurred in the upper uterine segment.

Now more hangs upon cesarean section than appears at first sight and there are other things which should be said. Hysterectomy may be performed after the second operation, or at the request of the patient's family and her physician. In one clinic[18] hysterectomy is performed in women over 35 years of age in instances of abnormal menstruation. In another,[19] one woman in every five who have cesarean sections has her uterus removed; the majority of them are less than 38 years of age. If the patient is 40 years old, bilateral removal of the adnexa is advised; if less than that, in the event that both ovaries are normal, the right ovary is removed in order to reduce the chance of ovarian carcinoma. Contrariwise, Marshall,[20] who was impressed with the dangers of anesthesia in cesarean section, was of the opinion that uncontrollable hemorrhage may be the only indication for cesarean hysterectomy.

For the most part women do not accept another cesarean section with equanimity. Though the prospect is not as terrifying as it was a generation ago, many shrink from operation as unnatural and another pregnancy is unduly postponed. Parity is definitely limited. In any large number of repeat operations the number of women having the third baby by cesarean section is comparatively small. Mills[21] observed, in his experience in a hospital in Birmingham, England, where about 300 cesarean sections are performed every year, that remarkably few of these women come back to the hospital for a second baby. We need information on this point.

Perinatal Risk

It is easy today to make out a case for cesarean section. And it is not altogether surprising that, at the present moment, a new interest is being taken in its perinatal mortality. In San Francisco[22] with an incidence of cesarean section of 9.6 per cent, the perinatal mortality rate closely approaches the rate of vaginal delivery. And in Los Angeles with an incidence of cesarean section of almost 10 per cent, the rate has been lower than that of pelvic delivery. The current practice of the New York Lying-In Hospital, thoughtfully and carefully reported by Landesman,[23] emphasizes, to some extent, the nature of the problem. Though the infant mortality of cesarean section still remains twice the figure for their total clinic, very considerable reduction in the fetal mortality of cesarean section has been brought about by a 50 per cent increase in the incidence of abdominal delivery.

In this series of 2,714 births by cesarean section in Brooklyn, the perinatal mortality rate was 49.4, in terms of 1,000 live and stillbirths reported as of 20 weeks' gestation and over. In the entire City of New York, the same

year, there were 8,408 cesarean sections with 175 fetal deaths and 251 neonatal deaths during the first week of life, a total infant loss of 5 per cent. From 1950 to 1954, inclusive, in New York City the perinatal mortality rate for cesarean section has averaged 54.9, a figure 56 per cent above the general rate.

Fetal salvage is not the only issue of importance, yet it is a fact that in placenta previa operation may be postponed until the fetus has a reasonably good chance of life. Premature separation of the placenta threatens the life of the fetus far more than placenta previa. When separation is severe, delay in delivery is hazardous; if moderate, and the fetus is thought to be in distress, though viable, immediate operation should reduce fetal mortality. When, because of prior abdominal delivery, cesarean section is elected, proper timing of the operative procedure, which appears to be troublesome, is of the greatest importance. Much, but not all, of this component of neonatal mortality is associated with prematurity. Though this principle is rather widely accepted, it appears to be disregarded often in practice.

Conclusion

The rising incidence of cesarean section is a phenomenon in itself worth noting. It will provide ground for controversy, development by disciples and assault by critics. The astonishing progress made in reduction of maternal mortality rates and the belief that the perinatal death rate will be similarly lessened by unrestricted abdominal delivery join forces to diminish our fear and increase our complacency.

It is of prime importance to remember that the growing incidence of cesarean section is largely due to the pyramiding of this operation as an indication for another. In this series it accounted for at least 38.7 per cent of all cesarean sections. This figure was in the neighborhood of 1 per cent in 1940.[24]

Reflections on the dictum, once a cesarean always a cesarean, suggest that it might not be unprofitable to give a little thought to the connotations that these words have acquired. Whatever else may be said, what has been called a dictum is not a rash and unsubstantiated generalization. To some it appears solid and sensible. Others, though they are not unwilling to look facts in the face, minimize the risk of rupture, pointing to their own experience in permitting pelvic delivery, though they hedge each decision about with reservations. It may be said in some quarters that, since the risk of rupture is so slight, it does not matter. It does matter. The patient is not an impersonal unit in an impersonal group; what happened to others may happen to her. Other than the risk of death, which grows steadily less, the principal hazard of cesarean section is, perhaps, the scar in the uterus. Perhaps "once a cesarean, what next?" would point to the serious nature of the first operation.

It is not possible to reconcile opposing views, nor is that, at the moment, of first importance. Whether minimal maternal mortality justifies unrestricted cesarean section is a proper question. It appears, at any rate, that its peri-

natal mortality may be reduced, since nearly two-thirds of all the perinatal deaths in this series were associated with antepartum hemorrhage and previous cesarean section.

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32 Remsen Street

VAGINAL SMEARS IN PREGNANCY

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THERE has been a great deal of interest recently in the atypical epithelial hyperplasia which frequently occurs in the cervical epithelium during pregnancy.

Excellent articles have been written by Carrow and Greene,[1] Epperson and Hellman[2] describing in detail the changes the pregnant cervix may undergo. Carrow and his group believe that once the histological criteria for intraepithelial carcinoma of the cervix are present this diagnosis is valid despite the fact the patient is pregnant. Epperson and Hellman feel, however, that many of the changes in the pregnant cervix will revert to normal. Epperson had five cases in which the changes were typical of intraepithelial carcinoma, but on prolonged follow-up the epithelium reverted to a normal pattern. Hellman has added two similar cases to this study.

The majority of writers on this subject all agree that there are specific changes that take place in the pregnant cervix. This change can best be described as one of marked hyperactivity. The cervical glands become enlarged with increased secretions. The fibrous tissue and muscle bundles hypertrophy. There is a marked increase in the blood supply and lymphatics. The mucosa shows marked invasion by leukocytes. The basal layer of the epithelium shows more mitotic activity than in the nonpregnant state. The cells become irregular in size and shape and the nuclei change in their staining quality. It is understandable that on biopsy the sections may show a lesion similar to intraepithelial carcinoma.

In 1953 we began a screening program of all patients registered in the prenatal clinic, using the Papanicolaou vaginal smear technique. Our objective was to detect by vaginal smear the cases with atypical epithelial activity and to follow them through pregnancy and the postpartum period with serial smears. In this manner we planned to evaluate the significance of the atypical epithelial changes that occur.

Material and Methods

The material in this study is composed of all patients coming to the clinic. There was no selection. Our plan was to take vaginal smears using the Ayre spatula. The scrapings were then smeared on clean glass slides and placed in the alcohol and ether fixative and stained using the Papanicolaou technique.

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The smears were classified according to the Papanicolaou method, Classes I through V. Classes I and II are considered negative, Class III suspicious, and Classes IV and V positive.

Each patient had vaginal smears taken in the first, second, and third trimesters of the pregnancy and on the first postpartum visit made at eight weeks.

If all vaginal smears throughout pregnancy and the postpartum course were negative the patient was discharged from the study. If the patient had a suspicious or positive smear during pregnancy which persisted post partum or if the suspicious or positive smear appeared post partum a set routine was followed.

The vaginal smear was repeated in one month. If negative the patient was discharged from the study. If the smear was again reported as suspicious or positive it was repeated after a one-month interval. If the third smear was suspicious or positive, the patient was admitted to the hospital for dilatation, curettage, and cold knife cone biopsy of the cervix. Any epithelial changes in the cervix due to pregnancy should have reverted to normal five months post partum.

If there was a highly suspicious gross lesion on the cervix at any time during the study a punch biopsy was taken. Benign-appearing lesions such as erosions were not treated until the series of vaginal smears were completed.

We feel that a generous knife cone biopsy of the cervix is indicated. Our method has been to expose the cervix and place a suture through the lateral aspects on each side. We do a wide cold knife conization of the cervix. Lateral sutures act as hemostatic ligatures when tied. A large piece of Oxycel is placed at the cervix and the vagina is loosely packed with a gauze sponge which is removed in twenty-four hours.

Once the specimen is removed it is immediately pinned onto a strip of cardboard with the epithelial surface up and placed in formalin and fixed. We find that submitting large tissue specimens with good orientation offers the pathologist considerable aid in making a complete histological examination and diagnosis.

Results

Early in the study it became obvious that the goal of vaginal smears in each trimester and one post partum was not to be reached. We had to be satisfied in some cases with one smear in the prenatal period and the postpartum smear, but the majority of the patients had at least three smears, two in the prenatal period and one post partum.

In computing the results to date, we found that we had 1,010 patients. Of the 1,010 patients, 330 were lost to follow-up. Thus we have a total of 680 patients in the completed series with a total number of 2,099 vaginal smears examined.

Among the 680 cases, there were 17 cases in which the vaginal smears were suspicious or positive. In 7 of these cases the vaginal smear reverted to Class I in the allotted time. These cases will be closely followed with vaginal smears at three-month intervals. In 10 cases (Table I) the smear remained positive, necessitating hospitalization for dilatation, curettage, and biopsy of the cervix. Of the 10 cases subjected to biopsy, 3 were reported as chronic cervicitis, one chronic endocervicitis, and one atypical squamous metaplasia with basal-cell hyperplasia. Of the remaining 5, 4 were reported as carcinoma in situ and one Stage I epidermoid carcinoma of the cervix. These 5 cases give us an incidence of 0.75 per cent.

One patient in this series, not included in the table, showed a Class I smear during her pregnancy, but a year later on routine gynecological check was found to have a Class IV smear. Cervical biopsy showed an epidermoid carcinoma of the cervix, Stage I. On review of the vaginal smears taken during pregnancy, it was found that they should have been read as positive. If we were to include this case in our series, our incidence would rise to 0.88 per cent.

TABLE I

CASE	AGE	GRAVIDITY	PRENATAL SMEARS	SMEAR POST PARTUM EIGHT WEEKS	POSTPARTUM COURSE	DIAGNOSIS
1	24	i	Class I	Class IV	Class III, Class III	Curettage, biopsy Chronic cervicitis
2	29	i	Class I	Class III	Class III, Class III	Curettage, biopsy Chronic cervicitis
3	33	iv	Class IV Class IV	Class IV	Class IV, Class IV	Curettage, biopsy Carcinoma in situ
4	23	i	Class I	Class III	Class III, Class IV	Curettage, biopsy Epidermoid carcinoma, Stage I
5	35	v	Class I	Class III	Class III, Class III	Curettage, biopsy Carcinoma in situ
6	29	viii	Class III Class I	Class III	Class III, Class III	Curettage, biopsy Chronic cervicitis
7	27	vi	Class I	Class IV	Class III, Class III	Curettage, biopsy Atypical squamous metaplasia with basal-cell hyperplasia
8	31	vii	Class I	Class IV	Class III, Class III	Curettage, biopsy Chronic endocervicitis (pregnant again, Class I)
9	24	iii	Class III	Class III	Class IV, Class IV	Curettage, biopsy Carcinoma in situ
10	23	iv	Class III Class III	Class IV	Class IV, Class V	Curettage, biopsy Carcinoma in situ

Comment

The problem of carcinoma of the cervix in pregnancy and its early diagnosis by vaginal smear is one of great interest. We found in this series the patients presented no signs or symptoms of cancer. The 5 cases with positive biopsies had clean, normal-appearing cervices. The only positive clue we had was the abnormal vaginal smear. We feel that these lesions would have been missed if these patients had not been part of this study. There were no gross lesions during the pregnancy.

The cases in which the patients presented a suspicious or positive smear with negative biopsy will be followed with vaginal smears at monthly intervals and through subsequent pregnancies. In this manner we plan a long term follow-up.

In comparison with our incidence of 0.75 per cent, the incidence of carcinoma of the cervix in pregnancy is variously reported in the literature. Cuyler and associates[3] reported 0.06 per cent; Vara[4] at the University of Helsinki, 0.02 per cent; Philadelphia General Hospital[5] from July, 1949, to July, 1950, one cancer in 1,115 pregnancies; Hirst,[6] 0.09 per cent; Johnson and Weinfurtner,[7] 0.056 per cent; Epperson,[2] 0.1 per cent; Faulkner,[8] 0.73 per cent; Haynes, Brown and associates,[9] 0.53 per cent. Although our series at the Hartford Hospital is small we feel our incidence is significant. We do not feel we are justified in making any fast rule from this series as yet, but the results indicate that a routine postpartum vaginal smear would be a valuable aid in the diagnosis of early cases of cervical cancer.

Summary

Six hundred eighty obstetrical patients were followed during the prenatal and postpartum course. A total of 2,099 vaginal smears were taken and examined. Seventeen cases presented positive vaginal smears. In 7 cases the smear reverted to negative. Ten cases were subjected to biopsy. Three biopsies were reported as chronic cervicitis, one as chronic endocervicitis, and one as atypical squamous metaplasia with basal-cell hyperplasia, 4 as carcinoma in situ, and one as invasive carcinoma, Stage I. The incidence at the Hartford Hospital is 0.75 per cent. This is higher than in most clinics but we feel it is due to the small series at the present time. The problem of carcinoma of the cervix during pregnancy is discussed. A plea is made for a vaginal smear post partum.

I wish to thank Dr. Robert Tennant and Mrs. Elizabeth Wheeler for their invaluable aid in preparing this paper.

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ATYPICAL CELLULAR CHANGES IN ENDOMETRIAL GLANDS ASSOCIATED WITH ECTOPIC PREGNANCY*

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OUR attention was drawn to the atypical cellular changes in endometrial glands which may accompany pregnancy by the recent publication of Arias-Stella[1] and the opportunity, at approximately the same time, of examining a postabortal curettage specimen which exhibited these alterations to such a marked degree that a diagnosis of adenocarcinoma was considered (Figs. 1-4). Although some gynecologic pathologists were aware of these changes, there has been little reference to them in the literature and in the standard textbooks. Deelman[2] attributed them to a combination of inflammatory and degenerative processes. Arias-Stella has found that these alterations occurred in the absence of inflammation, however, and has observed them in abortions, hydatidiform moles, chorioadenoma destruens, choriocarcinoma, "syncytial endometritis," and ectopic pregnancy (one case). He came to the conclusion that these changes likely resulted from the hormonal activity of chorionic tissue. Ferguson[3] remarked on these nuclear changes, noting that they frequently accompanied abortions, and stated that such cells could conceivably be misinterpreted as carcinoma cells in vaginal smears.

These atypical cellular changes in endometrial glands associated with pregnancy consist primarily of nuclear and cellular enlargement. The nuclei may be as much as four to five times the normal size, are hyperchromatic, and may assume bizarre lobulated and elongated shapes (Figs. 3, 4, 8). Accompanying the alterations in nuclear morphology, there may be a loss of cellular polarity (Figs. 2, 3). The abnormal nuclei often tend to occupy the distal (luminal) portion of the cell. These atypical changes tend to be focal (Fig. 2). They may involve one or more cells in a single gland, or may involve the majority of the cells in several adjacent glands (Figs. 2, 11). This latter characteristic makes it necessary at times to examine several sections before the changes are recognized. Large vacuoles may occasionally be observed in the cytoplasm (Fig. 5). No nuclear alterations in the endometrial stromal cells have been noted by us nor, to our knowledge, recorded in the literature.

The diagnosis of ectopic pregnancy is usually made on the basis of the clinical findings. Microscopic examination of uterine curettements has been found to be of limited value. Romney, Hertig, and Reid[4] found a decidual type of endometrium in only 19 per cent of a series of 115 women with proved ectopic pregnancies. In their series, then, only one out of five women with

*Presented at a meeting of the Chicago Gynecological Society, Nov. 18, 1955.

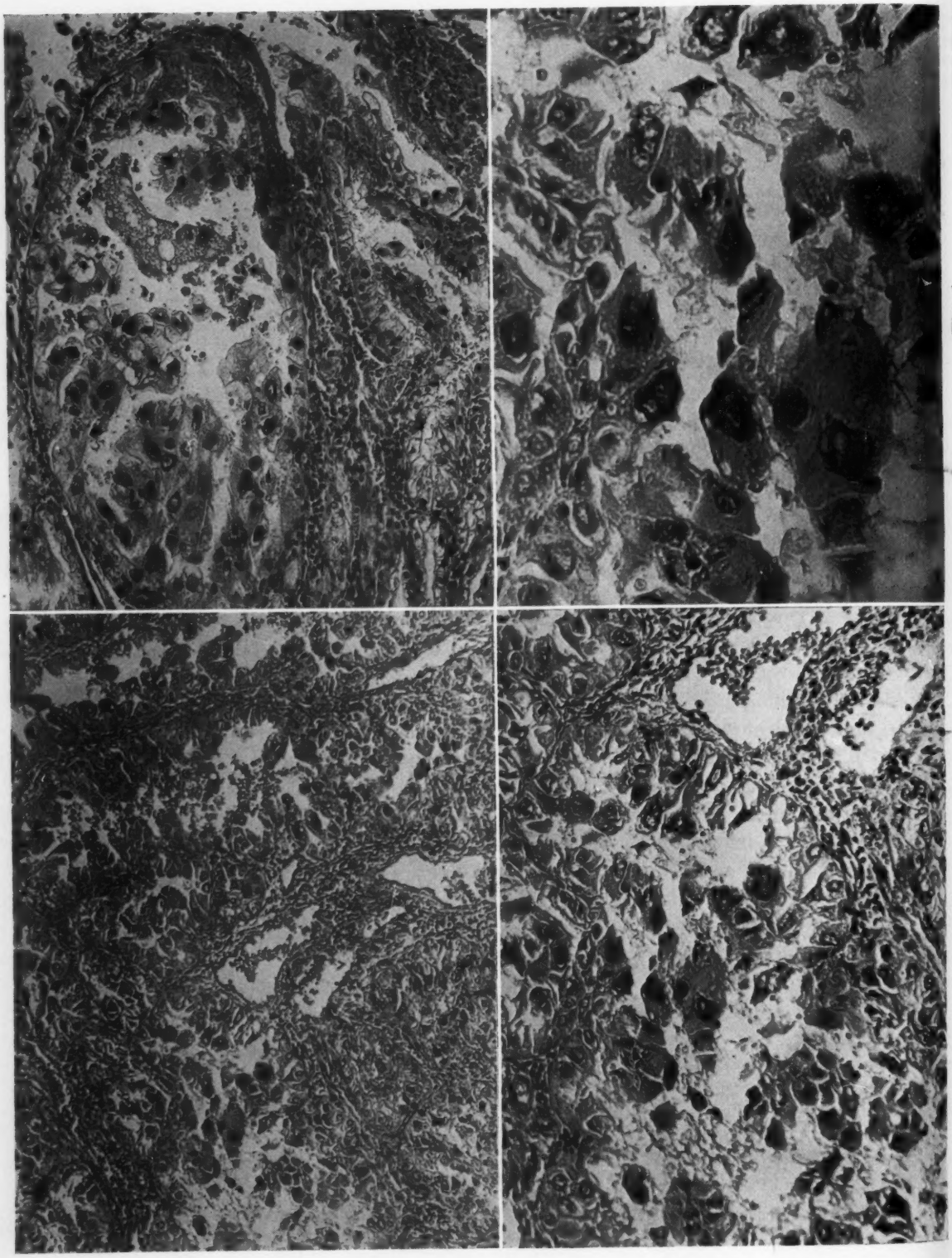


Fig. 2.

Fig. 1.

proved ectopic pregnancy had endometrial changes suggestive of pregnancy. We felt that it would be worth while to review the endometrial curettements from women with proved ectopic pregnancies treated at the Mount Sinai Hospital in an attempt to ascertain how frequently the atypical endometrial changes were present and to attempt to determine whether these changes are of practical value in the diagnosis of ectopic pregnancy.

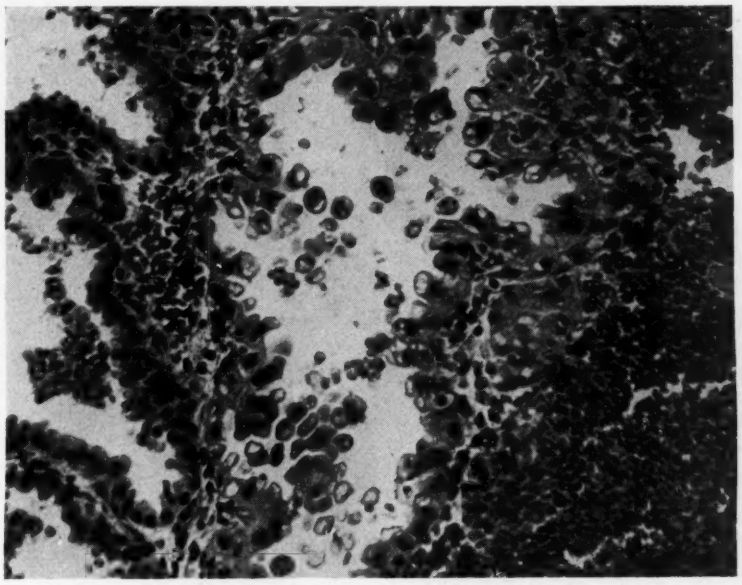


Fig. 5.—(MSH No. 51-1294. Vacuolization of the cytoplasm is marked in some examples of the atypical epithelial changes. (×415; reduced 1/10.)

Materials and Methods

All cases of pathologically proved ectopic pregnancy seen at Mount Sinai Hospital from January, 1946, to December, 1954, were reviewed. During this period there were a total of 121 cases. Endometrial curettements were available in only 50 cases, however. The latter 50 cases form the basis of the present study. In 48 of these cases, the implantation site was in the Fallopian

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Fig. 1.—(MSH No. 54-3601.) Marked atypical epithelial changes in endometrial glands in a curettage specimen following a spontaneous abortion. The patient, a 24-year-old woman, gravida 1, para 0, entered Mount Sinai Hospital in June, 1954, complaining of lower abdominal cramps and vaginal bleeding of 12 hours' duration. Her last normal menstrual period was approximately two months prior to admission. The past menstrual history was not remarkable (menarche at age of 12; periods every 27 days, lasting 4 to 5 days with some dysmenorrhea). On the day following admission, some placental tissue and fetal membranes were spontaneously passed. A curettage was performed. The pathologic diagnosis was hyperplastic pregnancy reaction and it was recommended that a curettage be performed at a later date so that the endometrium could be studied when not influenced by the presence of chorionic tissue. The patient was readmitted to the hospital two months later for the follow-up curettage. The interval history was not remarkable. The curettage specimen showed a normal proliferative endometrium. In June, 1955, the patient delivered a normal male infant. (×160; reduced 1/10.)

Fig. 2.—(MSH No. 54-3601.) The atypical epithelial changes tend to be focal in distribution. There is also loss of cellular and nuclear polarity. Same case as Fig. 1. (×168; reduced 1/10.)

Fig. 3.—(MSH No. 54-3601.) Higher magnification showing the scantiness of the intervening stroma and the loss of cellular polarity in the endometrial glands. Same case as Figs. 1 and 2. (×450; reduced 1/10.)

Fig. 4.—(MSH No. 54-3601.) The nuclei vary greatly in size and there are bizarre nuclear forms. Same case as Figs. 1, 2, and 3. (×750; reduced 1/10.)

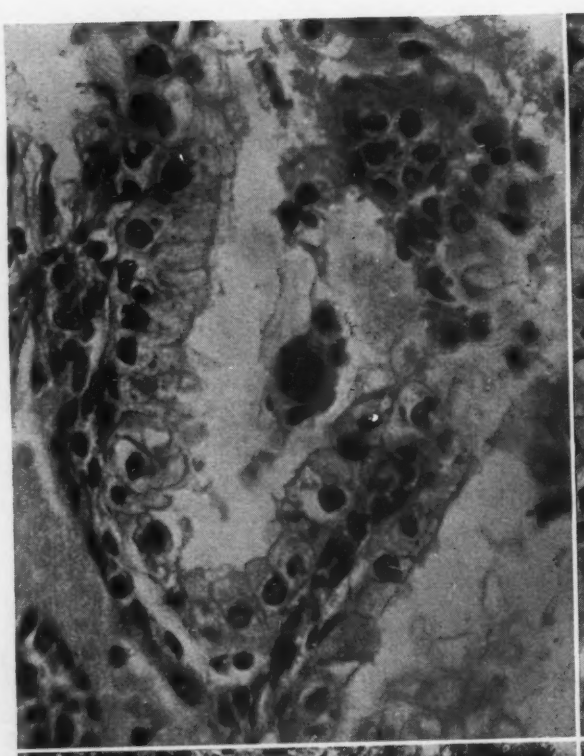


Fig. 7.

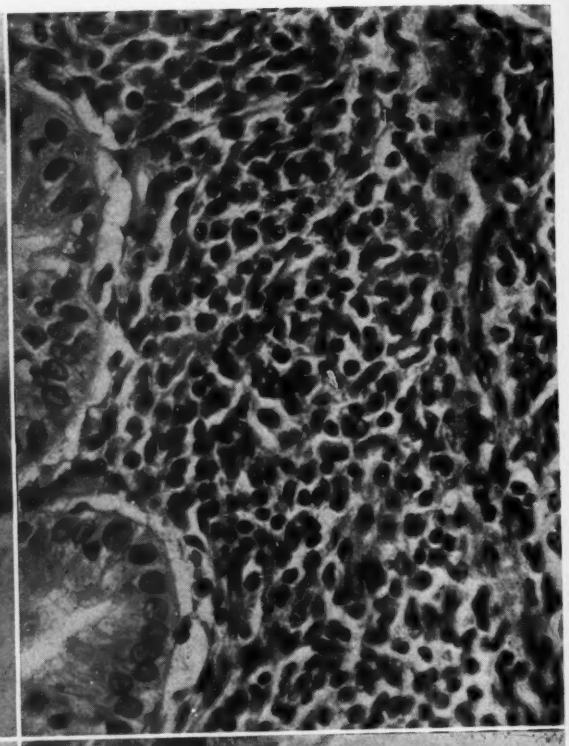


Fig. 9.



Fig. 6.



Fig. 8.

tube. The ovary and the serosal surface of the uterus were the implantation sites in two cases. As a control study we reviewed sections from 25 consecutive hysterectomy specimens with a secretory endometrium and 25 consecutive hysterectomy specimens with a proliferative endometrium that were received in this laboratory for the presence of atypical endometrial changes. Since the Fallopian tubes and ovaries were also removed in the majority of these control cases, or at least had been inspected by the surgeon and had not been removed because they appeared normal, it is felt that the possibility of an unrecognized pregnancy in this control series is very remote. Fifty endometrial specimens which contained chorionic villi or placental-site giant cells were also reviewed for the presence of atypical changes in the endometrial glands. This latter group included one case of transitional hydatidiform mole.

Results

The review of the endometria from the 50 hysterectomy specimens in which the possibility of pregnancy had been ruled out failed to disclose evidence of atypical changes in the endometrial glands in any of the cases. The study of the sections made from the curettements obtained following incomplete abortion and containing chorionic villi or placental-site giant cells revealed atypical changes to be present in the endometrial epithelium in 34 out of 50 cases (68 per cent). The histologic findings of the endometria of the 50 women with ectopic pregnancies are summarized in Table I. It can be seen that a decidual reaction in the endometrial stroma without the presence of chorionic villi or placental-site giant cells was observed in 42 per cent of the cases. The presence of a well-developed decidual reaction without chorionic villi or placental-site giant cells in numerous sections taken at various levels through the curettage specimen may be accepted as suggestive evidence of an extrauterine pregnancy, although it must be recognized that the possibility of an intrauterine pregnancy is not excluded, and that on rare occasions certain ovarian lesions may exert an excessive progestational effect on the endometrium with the formation of a decidual type of endometrial stroma. The finding of greatest interest in this study, however, lies in the group of patients with secretory endometria without decidual reaction. Admittedly it is extremely difficult, and in many cases impossible, to distinguish between a late secretory endometrium with a marked pseudodecidual reaction in the stroma and the endometrium associated with an early pregnancy. Criteria that may be of value in suspecting the presence of an early pregnancy are the simultaneous presence of active glandular secretion, stromal edema, and pseudodecidual reaction.[5] In the normal endometrial cycle active glandular secretion occurs in the early secretory phase, stromal edema in the mid-secretory phase, and pseudodecidual reaction begins in the late secretory phase.[5] The simultaneous presence of all three histologic features implies persistence of the corpus luteum. The persistence of the corpus luteum is associated, of course, in the vast majority of instances with

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Fig. 6.—(MSH No. 51-4872.) This is a curettage specimen from a patient with ectopic pregnancy. The endometrial glands are secretory in type and there is no decidual reaction in the stroma. Note the large nucleus in the endometrial epithelial cell near the upper center of the illustration. (×237; reduced 1/10.)

Fig. 7.—(MSH No. 51-4872.) Higher magnification of the nucleus referred to in Fig. 6. (×760; reduced 1/10.)

Fig. 8.—(MSH No. 51-4872.) Marked nuclear hypertrophy in an endometrial epithelial cell seen in association with ectopic pregnancy. It is conceivable that such nuclear changes could be interpreted as neoplastic. (×920; reduced 1/10.)

Fig. 9.—(MSH No. 51-4872.) Typical appearance of the endometrial stroma in the case illustrated in Figs. 6, 7, and 8. There is no evidence of a significant decidual reaction. (×700; reduced 1/10.)

Fig. 10.

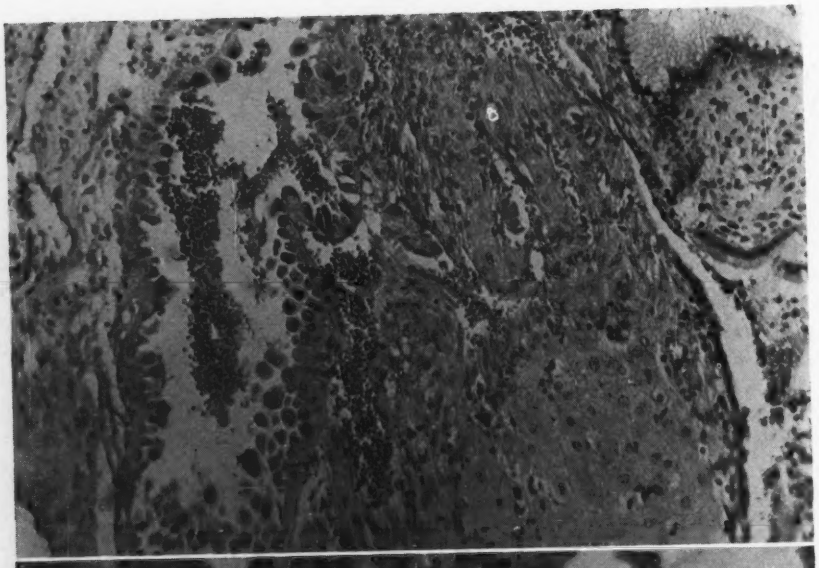


Fig. 11.

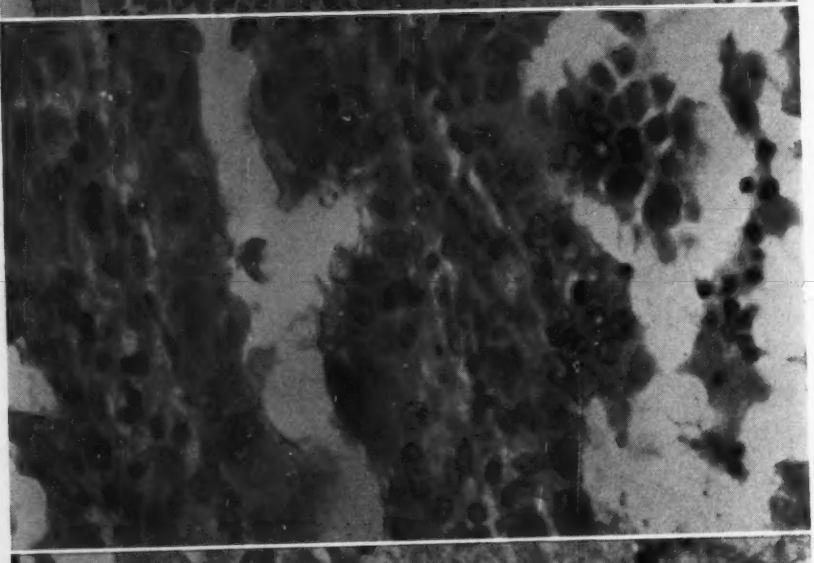
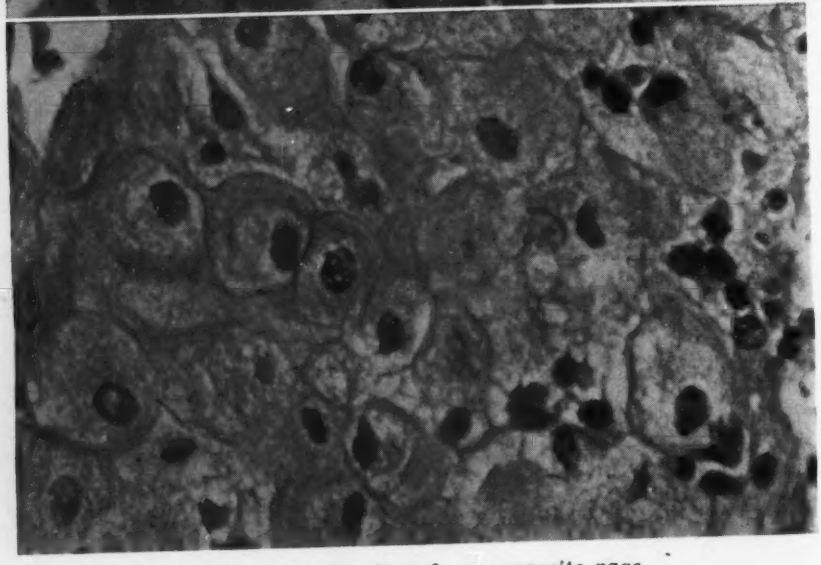


Fig. 12.



Figs. 10-12.—*For legends see opposite page.*

pregnancy. With these criteria in mind, 26 per cent of our series of 50 women with proved ectopic pregnancy were judged to have an endometrium in the secretory phase and to be without all of the features enumerated above which suggest an early pregnancy. Four out of 13 (31 per cent) of the latter cases, however, exhibited atypical nuclear changes of the type previously described, and presumably the presence of pregnancy could have been suspected had the pathologist been aware of the significance of these findings (Figs. 6-9). In the present series, then, it would have been possible to have suspected the presence of pregnancy from the histologic examination of the endometrial curettements in 50 per cent of patients with proved ectopic pregnancy, 42 per cent of the cases showing a decidual reaction in the endometrial stroma and 8 per cent showing a secretory endometrium with atypical nuclear changes in the endometrial epithelium.

TABLE I. ENDOMETRIA ASSOCIATED WITH ECTOPIC PREGNANCIES

TYPE	NUMBER	PER CENT	ATYPICAL CHANGES	
			NUMBER	PER CENT
Menstrual	1	2	0	0
Proliferative	15	30	0	0
Secretory	13	26	4	31
Decidual	21	42	9	43
Total	50	100	13	26

Comment

At the present time it appears most logical to regard the atypical changes in the endometrial epithelium referred to above as a hormonal effect. Inflammation appears to play no part in the histogenesis of this atypical endometrial pattern as the changes have been observed in areas in which there was no significant infiltration of inflammatory cells, and these alterations have not been reported in cases of marked endometritis not associated with pregnancy. We have no data that would enable us to correlate the presence or absence of these atypical features with the quantitative level of chorionic gonadotropin at the time of curettage. Recently, Arias-Stella[6] has been able to reproduce an apparently similar histologic pattern in rats by the simultaneous administration of human chorionic hormone and estrogen (estradiol). He was unable to produce these changes in ovariectomized rats when he administered human chorionic hormone and estrogen, but could produce these changes in ovariectomized rats by the administration of estrogen and progesterone.

In the present series of 50 women with pathologically proved ectopic pregnancy, changes in the endometrium suggestive of the presence of chorionic tissue were found in 25 (50 per cent). Twenty-one of the latter cases (42 per

Fig. 10.—(MSH No. 52-3892.) This is a curettage specimen from a patient with ectopic pregnancy with decidual reaction in the endometrial stroma. Note the atypical epithelial changes in the gland to the left of the center. (×210; reduced 1/10.)

Fig. 11.—(MSH No. 52-3892.) The same case as illustrated in Fig. 10. Note that the nuclear alteration involves a single cell in the gland. (×700; reduced 1/10.)

Fig. 12.—(MSH No. 52-3892.) Typical appearance of the endometrial stroma in the case illustrated in Figs. 10 and 11. There is a marked decidual reaction, the stromal cells contain abundant cytoplasm, and there is a refractile cell border. Compare with the appearance of the endometrial stroma illustrated in Fig. 9. (×1,000; reduced 1/10.)

cent of the entire series) showed a marked decidual reaction in the endometrial stroma without the presence of chorionic villi or placental-site giant cells in multiple sections, and 4 cases (8 per cent of the entire series) showed a secretory endometrium without a decidual reaction in the endometrial stroma or other changes suggestive of pregnancy. In this series of cases, then, a pathologist should have been able to suspect a pregnancy from the histologic appearance of the endometrium in 50 per cent of the patients. In the other 50 per cent of the patients there were no histologic changes that we were able to recognize which suggested pregnancy, and the obstetrician would have been misled in the management of these latter cases had he relied upon the laboratory rather than clinical evaluation. On the basis of this rather small series, it appears that a careful search for these atypical changes in the endometrial epithelium in curettage specimens from a patient suspected of having an ectopic pregnancy or suffering from uterine bleeding of unknown etiology will result in a somewhat higher percentage of cases in which the presence of a pregnancy can be suspected from histologic examination. The diagnostic value of the atypical epithelial changes appears limited principally to those cases showing a secretory endometrium without decidual reaction.

Summary

Cytologic changes in the endometrial epithelium consisting primarily of nuclear and cellular hypertrophy have been described and appear to be associated with the presence of chorionic tissue in either an intrauterine or an extrauterine site. In this report, a series of 50 patients with pathologically proved ectopic pregnancies in which endometrial curettage specimens were available was analyzed. The atypical epithelial changes were found in 43 per cent of the cases showing a decidual reaction in the endometrial stroma and in 31 per cent of those showing a secretory endometrium without decidual reaction. Considering all 50 patients in this series, 13 (26 per cent) showed atypical changes in the endometrial epithelium. It was found that in 50 per cent of the cases there were changes in the curettage specimen suggestive of pregnancy. In the other 50 per cent of cases the endometrial specimens showed no changes that could be interpreted as due to pregnancy. It is the small group of cases (8 per cent) in which the only histologic indication that a pregnancy was present was the presence of the atypical changes in the endometrial glands in which we are particularly interested in this report. It appears that a careful search for these changes in curettage specimens showing a secretory phase without decidual reaction in the endometrial stroma will result in the recognition of pregnancy in a slightly higher percentage of cases of ectopic pregnancy than if only a classical decidual reaction is considered as presumptive evidence of pregnancy. To our knowledge these atypical epithelial changes have always been associated with pregnancy. The incidence of the atypical epithelial changes appears to be higher in curettage specimens following incomplete abortion of an intrauterine pregnancy than in curettage specimens from patients with extrauterine pregnancy (68 per cent vs. 26 per cent in the present series).

We are indebted to Dr. S. J. Benensohn for permission to publish case No. 54-3601, and wish to thank Mrs. Evelyn M. Palmer of the Department of Illustration, Mount Sinai Hospital, who prepared the photomicrographs.

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Discussion

DR. R. R. GREENE.—Recently we had an argument in our laboratory at Northwestern University about the findings in a slide from the uterus of a patient with an ectopic pregnancy. The opinion was divided as to the exact nature of a small area in the endometrium. My own reaction at first was that it was an adenoma and even possibly an early carcinoma. Examination of other slides from the uterus, however, showed similar areas present in isolated glands. After reading a copy of this paper, we concluded that ours was an exaggerated example of the abnormalities that one can find in the endometrium of a pregnant patient. The findings in our patient were apparently similar to those that prompted the study by Dr. Pildes and Dr. Wheeler.

I recently checked the endometria from 20 patients with tubal pregnancies. The variability in the appearance of the endometrium from patients with tubal pregnancies is truly amazing. Be that as it may, my findings were similar to those reported by the authors. There were areas of atypical changes in the glandular epithelium in 11 of the 20 specimens. The atypia was variable in degree and extent. In each instance it was found in secretory areas or in endometria that had undergone a decidual reaction. With the exception of the instance cited, the abnormalities were relatively minor and not to be confused with cancer.

In essence, I have been able to confirm the findings of the authors. I wish, though, that they had presented their material as interesting pathologic findings, theorized as to cause, and then stopped right there. I doubt that their findings will be of practical or significant aid in the diagnosis of ectopic pregnancies. In the first place the authors have not studied the endometrium from patients with corpus luteum cysts. This is a condition which we have all unfortunately confused at one time or another with an ectopic pregnancy. It is conceivable that a similar atypia might be found in the endometria. In the second place, I suspect that very few of us would do a curettage and wait for the pathologist's report before proceeding further with a suspected ectopic pregnancy.

DR. JOHN I. BREWER.—I do not like to congratulate speakers for giving papers but I just must do it to these people because to me they are young, have an idea and imagination, and have followed it through, which is much more important than the practical aspect of the work. The observations they have shown are true. Whether it is practical or not makes little difference. Their thought that it may be hormonal stimulation is, of course, unproved but it is suggestive. Glandular epithelium can be altered markedly if there is inflammatory reaction, but they say there was none. Similar changes may be seen in a polyp where there was no inflammatory reaction and in a woman who was not pregnant. As Dr. Greene said, he has seen it and can confirm it. The slide Dr. Greene showed me one day in the laboratory, without too much stretch of the imagination, could be called adenocarcinoma and yet we did not think it was. As the authors demonstrate, the similarity may be close.

DR. A. F. LASH.—I think one more point should be added to those which have been presented. In addition to the fact that curettage showed endometrium with gross

decidual reaction and colpotomy shows no evidence of ectopic pregnancy, but the patient continues to spot, that patient needs further study. I have seen several cases where the bleeding was due to choriocarcinoma which was overlooked because it was not found on curettage, or was not found either in the tube or ovary but was in the uterine wall where the diagnosis could not be made except by hormonal test. I would say in the presence of such histologic findings that hormonal studies were warranted. If these studies revealed positive tests with undiluted urine, and especially in diluted urine, then one should think of the possibility of choriocarcinoma of chorioadenoma destruens.

DR. FREDERICK J. HOFMEISTER, Milwaukee, Wis.—I feel as Dr. Greene does that this is of very little practical value for application as a diagnostic aid. When the question of ectopic pregnancy arises the diagnosis must be made immediately. A case is recorded in our community where a patient was curetted for what was thought to be an incomplete abortion. Two days later she was sent home, and promptly died of intra-abdominal hemorrhage and shock. An ectopic pregnancy was overlooked and ruptured. A diagnosis in 50 per cent of the cases as possible, by evaluating cellular changes, leaves 50 per cent to conjecture. The real answer when the question arises is found by either opening the abdomen or using a more definitive type of diagnostic aid, colpotomy or colpocentesis.

DR. PILDES (Closing).—We do not recommend doing a dilatation and curettage to diagnose ectopic pregnancy when this condition is clinically suspected. The greatest value of recognition of these cellular changes lies in clinically unsuspected cases.

KYPHOSCOLIOSIS AND PREGNANCY

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CENTURIES before Christ, Hippocrates wrote, "Such persons as become humpbacked from asthma or cough (tuberculosis) before puberty, die." Kyphoscoliosis is an ancient affliction. Though discussed in continental European medical literature of the nineteenth and early twentieth centuries, it is in recent years that English and American workers have written about medical problems of the hunchbacked. Today, a good research bibliography of the subject, particularly as it pertains to pregnancy, includes articles by Chapman, Dill, and Graybiel,[1] Daley,[2] Dewhurst,[3] Fearl,[4] Jensen,[5] Mendelson,[6] and Webb and Harder.[7]

Long regarded as skeletal cripples, people with kyphoscoliosis have become well recognized as cardiac cripples. They are also gravely handicapped by their pulmonary deficiencies, having extremely deformed lungs of very limited capacity. There is a growing feeling among investigators today[3, 4, 7] that the primary kyphoscoliotic visceral incapacity is that of the lungs which are unable to provide proper oxygenation, causing strain and damage to the heart.

Incidence

Unusual and formidable is the case in which the stress of kyphoscoliosis is combined with the increased physiological demand of pregnancy. Yet within a seventeen-year period, from Jan. 20, 1939, through Nov. 26, 1955, MacDonald House of University Hospitals in Cleveland, Ohio, had 38 such cases involving 22 patients. These 22 were selected from a total of 84 cases of spinal deformities reported. The 66 cases not used were deformities of lesser degree without severe chest deformity. The number of pregnancies totaled 39, including one therapeutic abortion; one pregnancy not delivered at its maturity at MacDonald House; and 37 deliveries, among them one set of twins. During this period, MacDonald House had 54,445 deliveries. Thus, one out of every 1,471 maternity cases involved kyphoscoliosis.

TABLE I. CAUSES OF KYPHOSCOLIOSIS IN 22 MATERNITY PATIENTS

Unknown		11
Trauma		6
	Falls	3
	Birth	1
	Kicked by cow at age of 11	1
	Unspecified	1
Disease		5
	Tuberculosis	3
	Poliomyelitis	1
	Rickets	1

In contrast, Mendelson reported from New York Lying-In Hospital only 7 such cases in some 50,000 deliveries over a sixteen-year period, about one in 7,000. Among some 75,000 cases recorded by the University of Oregon Medical School and three affiliated hospitals in a ten-year period, Fearl found just 6 cases of pregnancy with kyphoscoliosis, about one in 12,000.

Data on This Series

Maternal Age.—Of the 22 women we are studying, the 2 youngest were 20 at the time of delivery; the oldest was 40. Fourteen patients in this series were under 30; 8 were over 30 at the time of delivery. According to Chapman and his co-workers, the average span of life for patients with scoliosis is 30 years. Mendelson considers age unimportant in regard to kyphoscoliosis with pregnancy. In Jensen's studies of 50 such fatal cases with kyphoscoliosis, the mortality rate under the age of 29 was 26.1 per cent; while 73.8 per cent of the deaths occurred in a group 30 years of age and older. In Fearl's series of 6 pregnancies with kyphoscoliosis, there was one death of a patient aged 41. In this series of 38 pregnancies with kyphoscoliosis, one patient did not survive. She was 36 years old.

Race.—Sixteen of the patients were white and 6 were Negro.

Vital Capacity Studies.—The severely twisted spine deforms the thoracic viscera. "All studies referable to vital capacity of the lungs in kyphoscoliosis show a marked diminution of this portion of lung volume," notes Fearl. "It is usually one-half that found in normal individuals. Along with this, the ratio of residual air to vital capacity is about double that of normal. The vital capacity will be 44 per cent of the total lung volume in the person with kyphoscoliosis and 63 per cent in the normal individual." Vital capacity studies made of 6 of our pregnant patients with kyphoscoliosis agreed with Fearl's statement.

The pregnant woman with kyphoscoliosis apparently manages despite her reduced vital capacity. In this series, a vital capacity approximately half that of normal was found in a woman with kyphoscoliosis, pregnant for the third time within four years. No obstetrical or other complications ensued. A 44-year-old pregnant woman with kyphoscoliosis, with a vital capacity of 47 per cent, gave birth to twins by breech delivery with no complications.

Dewhurst notes, "There is often rigidity of the thoracic cage [in kyphoscoliosis] with limitation of pulmonary expansion, whilst, at the same time, diaphragmatic flattening results in poor abdominal respiration. The respiratory exchange is inefficient, and the vital capacity is reduced." This is illustrated in one of our patients, a 31-year-old primigravida. When she was 14 weeks pregnant, her vital capacity was 83 per cent of normal. By the twenty-seventh week of pregnancy, the vital capacity had dropped to 35 per cent of normal, evidence that the rigid chest cage of the pregnant woman with kyphoscoliosis cannot adjust its respiratory volume as can the normal mobile chest cage to compensate for the tumor of pregnancy.

Fearl states that thoracic surgeons consider a vital capacity of 1,000 to 1,200 c.c. as the lower limit to which patients can descend without adding greatly to their surgical risk. The vital capacity study taken of the one patient in this series who did not survive her pregnancy, her third, was 600 c.c., well below the safe minimum.

Labor and Delivery.—How did women afflicted with kyphoscoliosis fare in labor and delivery? The average length of labor in 33 vaginal deliveries was 9¾ hours. The shortest was 1 hour, 11 minutes, a spontaneous delivery with gas and oxygen as analgesic and anesthesia. The longest labor was that of a 21-year-old primipara, who, at 26 weeks' gestation, was in labor for 34½ hours.

She delivered spontaneously a 26 week premature male infant that died the following day. Three years later she gave birth to a normal term male after 12 hours of labor.

TABLE II. METHODS OF DELIVERY IN 37 PREGNANCIES ASSOCIATED WITH KYPHOSCOLIOSIS

Spontaneous		5
Forceps		26
Low forceps	14	
Midforceps	12	
Breech extraction		1
Cesarean section		5

The high incidence of midforceps delivery was due to the wish to decrease the length of the second stage of labor. There were two primary cesarean sections, one for placenta previa, the other for a generally contracted pelvis. These 2 patients each had a repeat cesarean section. The cesarean operations were performed for obstetrical complications and not for any causes related to pulmonocardiac disease. One hysterotomy was done at 4½ months.

In this series, 5 postpartum tubal ligations were performed.

Morphine and Kyphoscoliosis.—Fearl notes Daly's now classic warning, published in 1945, against giving morphine to the kyphoscoliotic patient. "Not only is it dangerous from its respiratory effect, but when given to a patient in a position approaching the upright, the return of blood to the heart is hampered by peripheral dilatation of blood vessels," comments Fearl. In this series, 6 patients were given morphine as an analgesic with no observable ill effects. The latest use of morphine as an analgesic agent during labor occurred in August of 1948. Since that time, other preparations have been used in preference. Morphine was given during delivery to the one patient in this series of 22 who did not survive her pregnancy. A report of this case follows.

Case Report

A 36-year-old white woman, para ii, gravida iv, was first seen when she was about seven months pregnant. Her chief complaints were shortness of breath and a dry, unproductive cough.

Past History.—At 13 years of age, the patient developed a severe spinal deformity without any history of trauma. Kyphoscoliosis was ascribed to tuberculosis. At 25 years, the patient was told that she had "heart trouble" but she was asymptomatic until, at 32 years of age, she developed dyspnea on exertion. Dyspnea became increasingly severe during her thirty-fifth year. The patient had two normal uncomplicated pregnancies with rapid easy deliveries; one at 24 years, and one at 33 years.

First Hospital Admission.—On Dec. 9, 1948, she was admitted to the medical service of University Hospitals. Physical examination revealed a thin, middle-aged woman with a severe kyphoscoliosis of the dorsal spine. She was short of breath but in no apparent distress. Her temperature was 37° C., pulse 100, respirations 24, and blood pressure 125/75. There was slight distention of the neck veins; the lungs were clear to percussion with moist râles at both bases. There was increased precordial activity with cardiac dullness to the right and left anterior axillary lines. There was a harsh systolic murmur in the left interspace. From chest x-rays, the state of the heart and lungs, as in many such cases, was impossible to evaluate; but there appeared to be extensive old disease on the right, probably consisting of pleural thickening and fibrosis. Laboratory findings included: urine negative; hemoglobin 70 per cent; erythrocyte count 3.79 million; leukocyte count 10,000; micro precipitation test negative. Sputum examination was negative for acid-fast bacillus. The venous pressure was 90 mm. of water; arm to tongue circulation time, 19 seconds; arm to lung circulation time, 9 seconds; vital capacity, 600 c.c.

Hospital Course.—The patient was afebrile. She was digitalized with improvement of cough and shortness of breath. Moist râles at both bases did not clear. The patient was discharged after 11 days to be followed at weekly intervals in the obstetrical outpatient department. Dyspnea persisted with orthopnea. There was a slight ankle edema and chronic cough but no sputum. Treatment consisted of rest, digitalis, and sedatives.

Second Hospital Admission.—She was admitted on Jan. 13, 1949, to MacDonald House of University Hospitals. The findings were temperature 37° C., pulse 88, respirations 40, blood pressure 180/120. Physical examination was essentially as before. Rectal examination showed the fetal head to be in the pelvis at 0 station; the cervix was 4 cm. dilated, soft and thin. Urine examination showed albumin plus 2. At 8 A.M. the following morning uterine contractions began, occurring every 10 to 12 minutes and the patient was transferred to the delivery floor. The blood pressure was 145/80, pulse 120, respirations 28. Labor was fully established at 9:15 A.M. when the patient was given 100 mg. of Demerol and 150 grain of scopolamine. Contractions were occurring every 3 or 4 minutes. Routine scopolamine was given at 10 A.M., 10:45 A.M., and 12:15 P.M. At this time, because of restlessness, an additional 50 mg. of Demerol was given. At 1:45 P.M. the cervix was fully dilated and the patient was prepared for delivery by low forceps. A pudendal block anesthetic was given. Because of severe restlessness during delivery, ⅙ grain morphine sulfate was given intravenously.

A living male infant was delivered. Placenta and membranes were complete. The uterus was firm. There was no postpartum bleeding. At 2:30 P.M., 45 minutes after delivery, the findings were: pulse 122, respirations 24, blood pressure 148/80. At 3:30 P.M., one hour and 45 minutes after delivery, the findings were: pulse 100, respirations 20, blood pressure 180/100. The patient developed a generalized convulsion which lasted about three minutes. At 4:30 P.M., 2 hours and 45 minutes after delivery, the pulse was not obtainable, respirations were 14 and blood pressure 60/40. Respirations became slower and irregular; at 7:00 P.M. the patient died.

Autopsy Report.—The body weight was 43 kilograms. The heart weighed 338 grams and was normal in size and configuration. The right lung weighed 260 grams. The left lung weighed 415 grams. The lower lobe of the right lung was compressed. The upper lobe of the right lung was firm, the focus of fibrosis. Microscopic examination demonstrated a partial diffuse atelectasis and focal emphysema bilaterally. There was moderate passive hyperemia of the lungs and small foci of early bronchopneumonia in both lower lobes. The liver weighed 1,500 grams.

It is felt that this patient should have been hospitalized for the full period between her first hospital admission at seven months until delivery of her child; but home commitments blocked the possibility of such care. However, complete rest, diet, and protection from respiratory infection might well have enabled her to survive this pregnancy.

Dewhurst, reviewing Jensen's work, notes that he "collected from the literature 50 fatal cases of kyphoscoliosis complicating pregnancy. . . . It is clear that the majority of deaths were due to cardiorespiratory failure, and that true obstetrical complications accounted for a relatively small number. He found that there was a greater risk in those patients in whom the deformity was thoracic and who had previously had dyspnea. He concluded, also, that the risk was greater with increasing maternal age, and that the most dangerous period was the first twenty-four hours post-partum." This patient, suffering thoracic deformity and dyspnea and aged 36 years, died 5 hours after delivery. Statistically speaking, her chances for survival appear to have been heavily weighted against her from the outset.

Conclusions

1. Women with kyphoscoliosis compare favorably with those not so afflicted in their ability to conceive, to deliver vaginally, and to withstand successfully postpartum complications. Their grave thoracic deformities do not restrict their pelvic capacity for childbirth.

2. Vital capacity studies and chest films demonstrate that the patient with kyphoscoliosis is a pulmonary as well as a cardiac and skeletal cripple. Treatment should be directed toward prevention of overexertion and fatigue, control of weight gain, and sodium restriction in diet. The occurrence of pulmonary infection or evidence of cardiac failure must be treated actively by hospitalization.

3. Respiratory depressants such as morphine or its derivatives should not be given to patients with kyphoscoliosis. This restriction should not be confined to the obstetrical patient but should be repeated each year on the medical and surgical services and in the emergency ward of any general hospital.

4. In this series, 5 postpartum tubal ligations were performed. Tubal ligation may be offered mothers with kyphoscoliosis not so much because of the hazards of further pregnancies as because of the strenuous duties which child-rearing imposes upon these handicapped women.

5. One therapeutic abortion (abdominal hysterotomy) was performed at 4½ months. This patient had severe pulmonocardiac disease. We should have expected this patient to proceed through her pregnancy and a vaginal delivery without complications if adequate medical care with prolonged hospital stay could have been made available. We consider this case to be similar to that of any pregnant patient with severe rheumatic heart disease where vaginal delivery is less hazardous to the patient than a major surgical procedure during pregnancy.

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Gynecology

HISTOCHEMICAL TECHNIQUES APPLIED TO THE STUDY OF BENIGN AND MALIGNANT SQUAMOUS EPITHELIUM OF THE CERVIX UTERI*

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TODAY the attack on the cancer problem is manifold. Histochemistry is but one of numerous fields utilized in cancer research. Rather than stressing quantification as in biochemistry, histochemistry stresses accurate localization of chemical constituents. By correlating histochemical differences between normal and abnormal, it is hoped that morphological alterations may become more easily noted and interpreted.[64]

Definite diagnosis of very early malignant lesions of the cervix may be difficult or even impossible using present histologic techniques and morphologic criteria. It is primarily for this reason that the present histochemical study of the cervix was undertaken.

Material and Method

Cervices obtained at hysterectomy from 27 patients, including 5 with squamous carcinoma, were studied in detail. Four of the cancers were untreated and presented minimal or no necrosis; the fifth had been irradiated and showed no viable tumor cells. For specific diagnoses in these cases see Table III. An additional irradiated squamous carcinoma was reacted for only glucuronidase and phosphamidase. Except in this one case, reactions were carried out for: alkaline phosphatase, acid phosphatase, nonspecific esterase, sulfhydryl, disulfide, phosphamidase, glycogen-mucin, and glucuronidase. Stains were done for lipids (sudan B) and ribonucleic-desoxyribonucleic acids (methyl green pyronin).

The number of cervices subjected to each reaction is shown in Table I. In each case the entire cervix was amputated from the fresh surgical specimen (no later than ten minutes after removal from the patient) and accurately serially blocked in the fresh state at a thickness of 3 mm. by means of a special bladed knife as illustrated in Fig. 1. Fresh frozen sections were cut on a Sartorious cold knife microtome, dry mounted, and fixed in cold acetone or cold neutral 10 per cent formalin for varying periods of time depending on the reaction to be employed. The remainder of the block and all the other blocks were placed in acetone for 48 to 72 hours and embedded in paraffin, having first been passed through celloidin at 57° C. for 75 minutes in a vacuum oven.

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The celloidin-paraffin blocks were cut on a Spencer precision rotary microtome at 6 mm. (It is possible, however, to cut them on a sliding celloidin microtome.) Hereafter for the sake of brevity such sections will be referred to as paraffin sections.

In this manner a specific portion of tissue represented by contiguous sections could be studied with respect to all constituents; frozen sections could be compared with paraffin sections and both could be compared with a standard hematoxylin and eosin preparation of the identical area. Thus greater accuracy was achieved than was heretofore possible.

TABLE I. NUMBER OF CERVICES SUBJECTED TO HISTOCHEMICAL REACTIONS AND STAINS

TOTAL BENIGN	TOTAL MALIGNANT	REACTIONS STAINS	NORMAL PREMENOPAUSAL	NORMAL POSTMENOPAUSAL	LEUKOPARAKERATOSIS ANAPLASIA HYPERPLASIA	SQUAMOUS-CELL CARCINOMA
19	5	Glycogen-mucin	8	6	5	5
17	5	RNA-DNA	8	5	4	5
11	5	NSE (paraffin)	6	5	0	5
8	5	NSE (frozen)	2	2	4	5
16	5	ACP (paraffin)	7	5	4	5
9	5	ACP (frozen)	3	2	4	5
9	5	Glucuronidase	3	3	3	5
9	5	Lipids	2	3	4	5
16	4	SH-SS	8	4	4	4
11	4	ALP (paraffin)	6	5	0	4
8	5	ALP (frozen)	2	2	4	5
1	3	Phosphamidase (paraffin)	0	0	1	3
6	5	Phosphamidase (frozen)	2	3	1	5

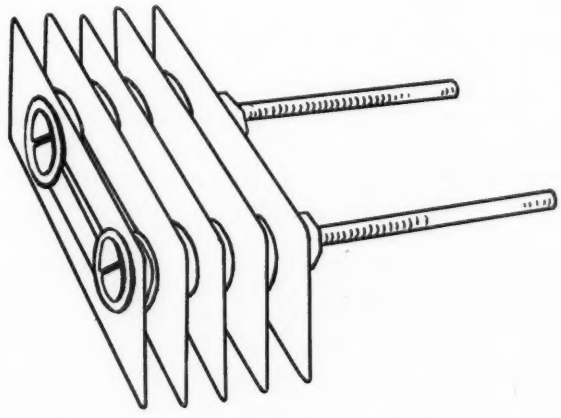


Fig. 1.—Simple multibladed knife which cuts fresh cervical blocks exactly 3 mm. thick. Razor blades were attached by two long screws and were separated from each other by flat metal washers.

It is important to stress that although the entire cervix in this series was studied by a rather complete battery of procedures, the total number of cases was few and therefore this paper represents but a preliminary report.

Specific Procedures.—

Lipids: A saturated solution of sudan black in 70 per cent alcohol was used to stain dry mounted frozen sections fixed 24 to 48 hours in cold buffered 10 per cent formalin containing calcium chloride. Phospholipids, glycolipids, and neutral fats are stained black.[55]

TABLE II. SIGNIFICANT ENZYMES OR SUBSTANCES IN THE BENIGN AND MALIGNANT SQUAMOUS EPITHELIUM OF 27 CERVICES REMOVED PRIOR TO OR AFTER THE MENOPAUSE

	PROLIFERATIVE		SECRETORY		MENSTRUAL		MENOPAUSAL		TOTAL NORMALS		LEUKOPARAKERATOSIS ANAPLASIA HYPERPLASIA		UNTREATED SQUAMOUS CARCINOMA	
	NO.	DEGREE*	NO.	DEGREE*	NO.	DEGREE*	NO.	DEGREE*	NO.	DEGREE*	NO.	DEGREE*	NO.	DEGREE*
											2	0-1+	3	0-1+
Glycogen	1	2+	1	2+	1	2+	1	2+	4	2+	1	2+	1	2+
	2	3+	2	3+	1	3+	5	3+	10	3+	2	3+		
Ribonucleic acid			2	0-1+	2	0-1+	3	0-1+	7	0-1+			2	0-1+
	2	2+	2	2+			2	2+	6	2+	2	2+		
											2	3+	2	3+
Nonspecific esterase														
Paraffin sections	2	0-1+	2	0-1+	1	0-1+	5	0-1+	10	0-1+			2	0-1+
	1	2+							1	2+				
													2	3+
Frozen sections			1	0-1+	1	0-1+	2	0-1+	4	0-1+	2	0-1+		
											2	2+		
													3	3+
Acid phosphatase														
Paraffin sections	3	0-1+	2	0-1+	2	0-1+	5	0-1+	12	0-1+	4	0-1+	1	0-1+
													1	2+
													2	3+
Frozen sections	1	0-1+	1	0-1+	1	0-1+	2	0-1+	5	0-1+	2	0-1+		
											2	2+	1	2+
													2	3+
Glucuronidase	3	0-1+					3	0-1+	6	0-1+	3	0-1+		
													2	3+

*Degree of intensity (1+ slight, 2+ moderate, 3+ marked).

Glycogen-mucin: Dry mounted paraffin sections were used. Glycogen is periodic acid Schiff (PAS) positive substance removed by saliva. The remainder, for the most part, is glycoprotein or mucin. Cellular constituents giving a positive Schiff reaction are the following: polysaccharides (glycogen), mucopolysaccharides, mucoproteins, glycoproteins, glycolipids, unsaturated lipids, and phospholipids. Because our attention was directed to squamous epithelium rather than the columnar cells of the endocervical glands, the possibility that some PAS positive material consists of noncarbohydrate substances was not considered of particular importance in this study and therefore differentiation was not attempted. In a recent cytologic study Hopman[31] reported that exposure of the reaction to heat permitted a differentiation between glycogen and mucin in columnar cells. When procedures were being standardized early in the course of our study we attempted to apply this method but without success. The difficulty is the large quantity of PAS positive, saliva resistant mucin produced by the columnar cells.[69]

Ribonucleic acid-desoxyribonucleic acid (RNA-DNA): Using dry mounted paraffin sections, ribonucleic acid and desoxyribonucleic acid were demonstrated by the methyl green pyronin method of Brachet.[55] Control slides were first exposed to ribonuclease. Material considered to be RNA stains red with pyronin and is removable by ribonuclease. Cellular constituents staining blue are DNA.

Sulfhydril-disulfide (SH-SS): Paraffin sections were treated in the manner described by Barrnett and Seligman[2] for protein-bound SH groups. Adjacent sections were reacted for both SH and SS.[3] The increase in intensity and differences in localization represent SS groups.

Alkaline phosphatase (ALP): Paraffin sections were reacted according to the method of Manheimer and Seligman[42] and were incubated for two hours. Frozen sections were treated in modified fashion and incubated 30 minutes.[55]

Nonspecific esterase (NSE): Paraffin sections were reacted according to the method of Nachlas and Seligman.[52] The incubation time was 2 to 3 hours. Frozen sections were handled in a modified manner and incubated for 15 to 30 minutes.[55] It should be noted that lipase, acetyl cholinesterase, nonspecific cholinesterase, and nonspecific esterase are all able to hydrolyze alpha naphthyl acetate.[55] Cholinesterase or lipase inhibitors were not employed.

Acid phosphatase (ACP): Paraffin sections were handled in two ways. One set of sections were treated according to Seligman and Manheimer.[59] The incubation time was 18 to 24 hours. To a second set of slides, incubated for 2 hours, Burton's[6] azo dye method was applied. Frozen sections were also treated by two methods: (1) Pearse's[55] modification of the Seligman and Manheimer procedure, for frozen sections. (2) Burton's method. Both were incubated 30 minutes.

Controls for esterases were provided by inactivation of enzyme by exposure to 10 per cent hydrochloric acid. Mounted frozen sections reacted for esterases were fixed in formalin for two hours; other sections from the same block were reacted unfixed. Coupling agents were selected so as to produce a clear-cut precipitate. Timing as well as other variable factors in the reactions were arranged so as to yield a light rather than heavy precipitate in minimally reactive areas.

Phosphamidase: Reactions for phosphamidase in paraffin sections were carried out according to the method described by Gomori.[22] Slight modifications, as noted before, were introduced for application to fresh frozen material. Paraffin-embedded tissue was fixed as usual for 24 to 72 hours and incubated in substrate solution for 4 to 12 hours. Mounted frozen sections were fixed in cold 10 per cent formalin 2 hours and incubated 4 hours. Controls were provided by preliminary exposure to Lugol's iodine solution.

Glucuronidase: This enzyme was demonstrated by a method described in 1954 by Seligman and associates.[61] Fresh mounted frozen sections were fixed for a maximum of 10 to 15 minutes in cold 10 per cent formalin and incubated 6 to 8 hours. Unfixed slides were treated in similar fashion. Because a specific inhibitor was not available, control slides were subjected to heat or incubated without substrate.

Observations

All slides were reviewed by the author several times to check subjective grading, indicated as follows: 1+ (slight), 2+ (moderate), and 3+ (marked). Close agreement was achieved in each review. Results according to intensity of reaction or staining appear in Tables II and III, and are summarized in Table IV.

TABLE III. DEGREE OF ACTIVITY OF NORMAL AND MALIGNANT AREAS IN EACH UNTREATED CARCINOMA

SIGNIFICANT STAINS AND REACTIONS	(1) CA. IN SITU		(2) INVASIVE CA.		(3) INVASIVE CA. IN PREGNANCY		(4) CA. IN SITU	
	NORMAL EPITHELIUM	CA.	NORMAL EPITHELIUM	CA.	NORMAL EPITHELIUM	CA.	NORMAL EPITHELIUM	CA.
Glycogen	3+*	1+	3+	0-2+	2+	1+	3+	1+
Ribonucleic acid	1+	2-3+	1-2+	2-3+	1+	1+	1+	1+
Nonspecific esterase								
Paraffin sections	1+	1+	1+	tr-3+	1+	1-3+	0	1+
Frozen sections	1+	v†	1+	1-3+	1+	3+	1-2+	2-3+
Acid phosphatase								
Paraffin sections	1+	1+	1+	3+	1+	3+	1+	2+
Frozen sections	1+	v†	1+	2-3+	1+	2+	1+	3+
Glucuronidase	1+	v†			1+	3+	1+	2-3+

*In each case the plus values are the maximal intensity.
† = Frozen section blocks had no cancer.

TABLE IV. SUMMARY: DEGREE OF ACTIVITY IN CERVICAL SQUAMOUS EPITHELIUM

STAINS AND REACTIONS	NORMAL	BENIGN	MALIGNANT
Significant Changes.—			
Glycogen	Marked	Slight	Slight
RNA	Slight-moderate	Moderate-marked	Occasionally marked
NSE	Slight	Slight-moderate	Marked
ACP	Slight	Slight-moderate	Slight-marked
Glucuronidase	Very slight	Very slight	Heavy
No Significant Changes.—			
Lipids	Slight		
DNA	Moderate		
SH-SS	Moderate		
ALP	Negative		
Phosphamidase	Variable		

Substances and Reactions Significant in Carcinoma of the Cervix

Such substances and reactions were glycogen, ribonucleic acid, nonspecific esterase, acid phosphatase and glucuronidase.

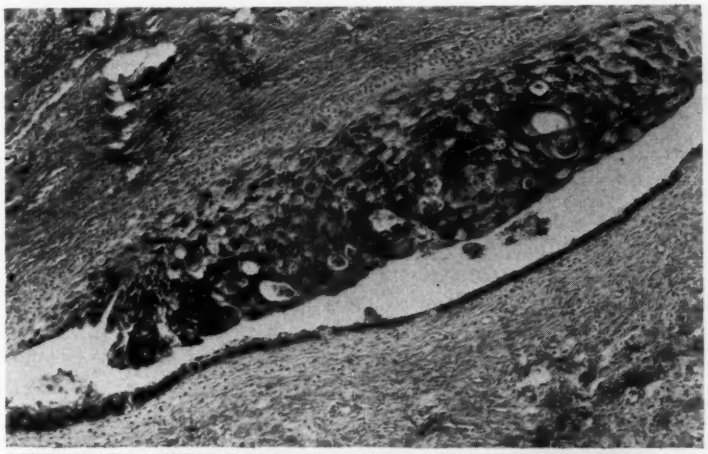
Glycogen.—

Squamous epithelium: The basal (germinal) layer had little or no glycogen. Focally there were traces at the peripheral margin of the cell. The overlying prickle (Malpighian) layer (2 to 5 cells thick) had more glycogen, arranged diffusely in the cytoplasm. Heaviest in glycogen content were the cells of the superficial layers. Especially deep staining were areas of parakeratosis. Glycogen content in squamous metaplasia and epidermization appeared to be correlated with the degree of differentiation of the cells (Figs. 2 and 3).

It was observed that, by decreasing the time of exposure to Schiff reagent, the thickness of the PAS negative layer increased, or conversely the positive area decreased.

Menstrual cycle: No correlation with the menstrual cycle was noted in squamous epithelium. The menopause appeared unassociated with diminished glycogen.

Fig. 2.



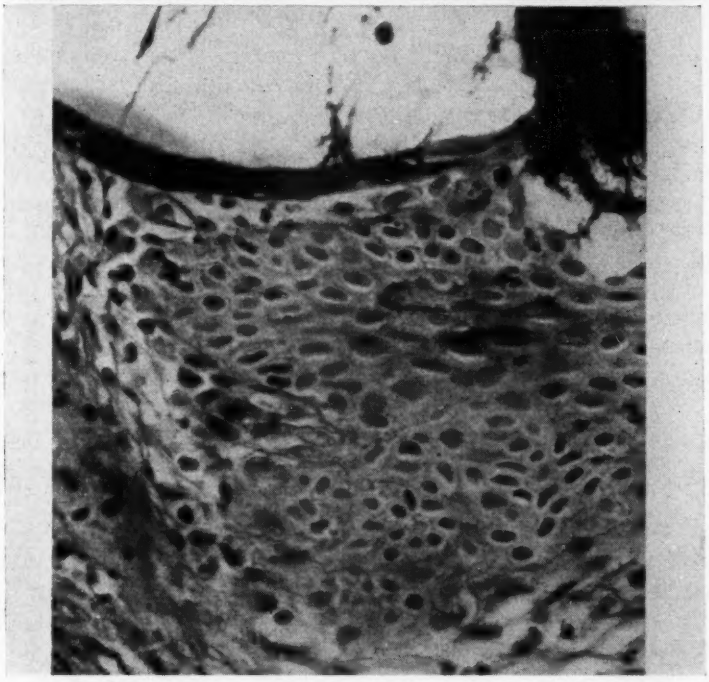


Fig. 3.

Fig. 2.—Path. No. 55-2272. PAS reaction showing glycogen in squamous metaplasia. The squamous cells are mature and PAS positive. (×130; reduced ¼.)

Fig. 3.—Path. No. 55-1515. PAS reaction in squamous metaplasia. The immature squamous cells lack glycogen. (×550; reduced ¼.)

Benign changes: No differences were observed in epidermoid hyperplasia per se. However, prickle-cell hyperplasia and anaplasia disclosed marked diminution in glycogen. An abrupt decrease occurred in leukoparakeratosis (Fig. 4).

Squamous carcinoma: There was a fairly sharp change at the junction of normal and malignant areas (Fig. 5). Squamous cancer had none to moderate amounts of glycogen depending on the maturity of the cells. Occasionally deeply staining parakeratosis, disappearing gradually, would continue over the malignant zone. Fig. 5 illustrates clearly that the cells of a carcinoma in situ are reminiscent of the basal rather than the prickle cell. When invasive carcinoma showed evidence of relative morphologic maturity a moderate amount of glycogen was not unusual. In irradiated cancer the mature cells had moderate quantities of glycogen. Pyknotic cells were only minimally PAS positive. The hyalinized surface was negative.

Summary of squamous changes: Whereas all of the 14 normal cervices had moderate to markedly positive squamous epithelium, one half of the benign, and almost all of the untreated malignant, lesions were at best only slightly positive for glycogen. In all cases, whether benign or malignant, the amount of glycogen present correlated well with the degree of differentiation.

Columnar epithelium: Whereas squamous epithelium was negative after salivary digestion the columnar epithelium of the endocervix remained strongly positive. Mucin and glycogen could not be differentiated inasmuch as there was slight or no significant difference between the digested and undigested slides. Although there was a tendency toward distal (luminal) cytoplasmic localization, many cells had a heavy and diffuse distribution of PAS positive material. Cyclic and menopausal changes could not be appreciated accurately with respect to either glycogen or mucin. There may be, however, a diminution after the menopause.[69]

Ribonucleic Acid.—Most RNA is contained in the cytoplasm and nucleolus which stained red with pyronin. DNA is limited almost exclusively to the nuclear chromatin and stained blue.

Squamous epithelium: Maximal intensity of staining occurred in the basal and prickle layers. Fine, punctate red droplets clustered about the sharply demarcated cell membrane. Not infrequently there was a diffuse distribution of precipitate which became coalescent in cells that had much RNA. Parakeratosis retained the stain prominently. The degree of staining in squamous metaplasia and epidermization appeared related to the degree of maturation of the particular cells. Particularly striking was the brilliant red cytoplasm of stromal plasma cells which are rich in RNA.

Menstrual cycle: No correlation with the menstrual cycle or menopause was noted.

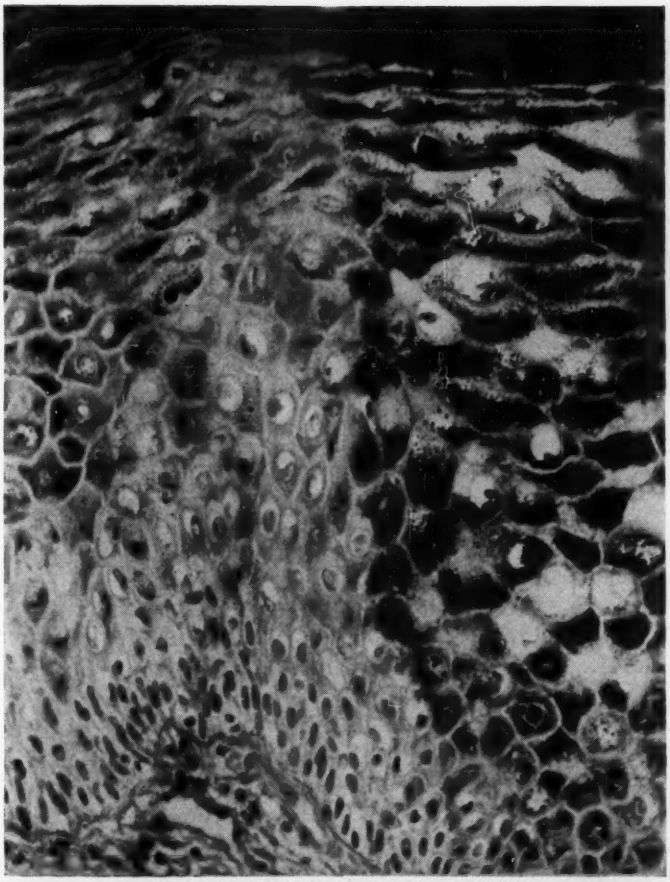
Benign changes: Patchy increased cytoplasmic RNA was observed in immature cells. Fig. 7 illustrates the change in leukoparakeratosis. Although there was no over-all change in epidermoid hyperplasia, prickle-cell hyperplasia and anaplasia revealed slightly increased RNA.

Squamous carcinoma: Some cases (Cases 1 and 2) had marked staining when compared to normal areas (Figs. 6 and 8). Others (Cases 3 and 4) disclosed no differences. Increase in the cytoplasmic RNA seemed to depend on the presence of immature basal type cells. Irradiated cancer cells were only slightly positive.

Fig. 4.—Path. No. 55-2175. PAS reaction in an area of leukoparakeratosis. Note the abrupt change between the PAS positive, glycogen-containing cells of the normal area on the right, and the weakly positive cells in the leukoparakeratotic focus on the left having scant glycogen. (×550; reduced ¼.)

Fig. 5.—Path. No. 55-2865. Carcinoma in situ. The change between the normal area on the left (rich in glycogen) and the malignant area on the right (almost negative) is as abrupt as in Fig. 4. The PAS negative cells of the carcinoma in situ are very similar to the basal cells of the normal area. (×550; reduced ¼.)

Fig. 4.



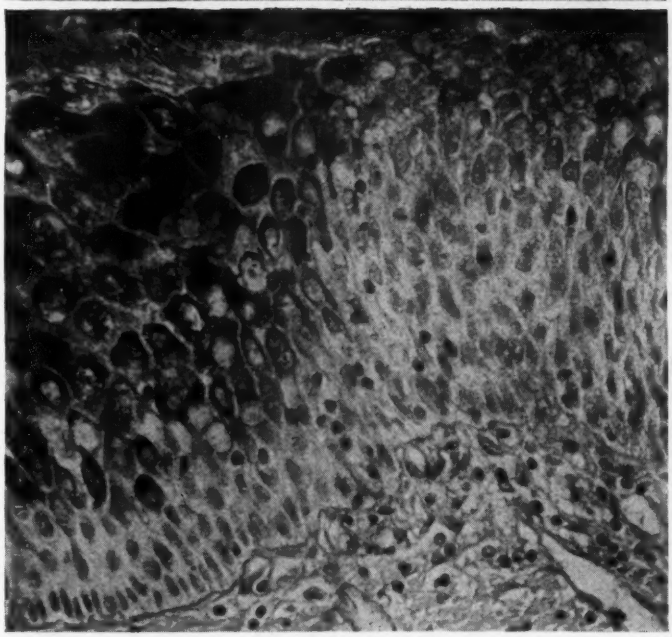


Fig. 5.

Figs. 4 and 5.—*For legends see opposite page.*

Summary of squamous changes: Of 13 normal cases 7 were slightly and 6 moderately positive. In the benign group one half were moderately and one half markedly positive. The malignant lesions were variable. Comparing malignant to normal areas, even in cases rich in RNA, there were variations in intensity of staining. Although in general morphologically immature cells appear definitely to have increased RNA, the variability is not entirely explained on a basis of differentiation. The correlation with maturation is an inverse one as compared to glycogen.

Columnar epithelium: There was a variable tendency toward concentration in the lumina. Glands were generally uniform in content. Occasionally the largest droplets of RNA appeared in a subnuclear localization. Whereas these disappeared in digested slides, smaller ones in a luminal distribution frequently remained after exposure to ribonuclease. Unlike squamous cells, columnar epithelium retained to a variable degree pink-to-red coloration in digested slides. There appeared to be no correlation with the menstrual cycle. A slight decrease of RNA occurred in the menopause.

Desoxyribonucleic Acid.—There were no appreciable nuclear DNA or nucleolar RNA changes in benign or malignant lesions other than the usual morphologic alterations.

Nonspecific Esterase.—Frozen sections had greater enzyme activity than paraffin sections. Unfixed frozen sections reacted much more intensely than those which had undergone preliminary fixation.

Squamous epithelium: In paraffin sections the reaction was generally slight and often negative. Particularly consistent was the relatively intense reaction in the basal layer. The largest droplets were clustered about the cell membrane. Intercellular bridges appeared to be black and quite prominent. Squamous metaplasia and epidermization presented no unusual reaction. Nuclei were frequently positive but these undoubtedly represented diffusion artifact. Frozen sections had similar localization but the reaction was heavier than in paraffin sections; the precipitate was more distinct, and nuclei were uniformly negative. Frozen sections brought out prominently the reaction in the granular layer. However, the largest and darkest droplets were in the basal layer, clustering about the margins. Superficially the reaction became more diffuse in the cytoplasm.

Menstrual cycle: No relationship to the menstrual cycle or to the menopause was observed.

Benign changes: Slight increased activity was noted. Leukoparakeratosis is illustrated in Fig. 9.

Squamous carcinoma: The over-all increase in activity was less marked in carcinoma in situ than in invasive carcinoma. All layers had definite elevation of NSE. Considerable diffusion, especially in paraffin preparations, occurred where the epithelial reaction was marked. Irradiated carcinomas disclosed minimal activity.

Summary of squamous changes: Almost every normal cervix had slight amounts of NSE; of the benign groups one half had slight and the other half moderate activity. In the untreated malignant cases, most had a moderate to

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Fig. 6.—Path. No. 55-2865. Ribonucleic acid in normal cervical squamous epithelium occurs mainly in the basal and prickle-cell layers (Malpighian). Brachet's methyl green pyronin method. (×550; reduced ¼.)

Fig. 7.—Path. No. 55-2175. Ribonucleic acid in leukoparakeratosis. In almost all layers there is an abrupt increase in cytoplasmic RNA. The normal zone toward the right stains very lightly. (×550; reduced ¼.)

Fig. 8.—Path. No. 55-2865. Ribonucleic acid in carcinoma in situ. Compare this area, staining very heavily, with Fig. 6 which shows a normal zone in the same specimen. Both areas were within several high-power fields of each other; the transition was gradual. (×550; reduced ¼.)

Fig. 6.

Fig. 7.

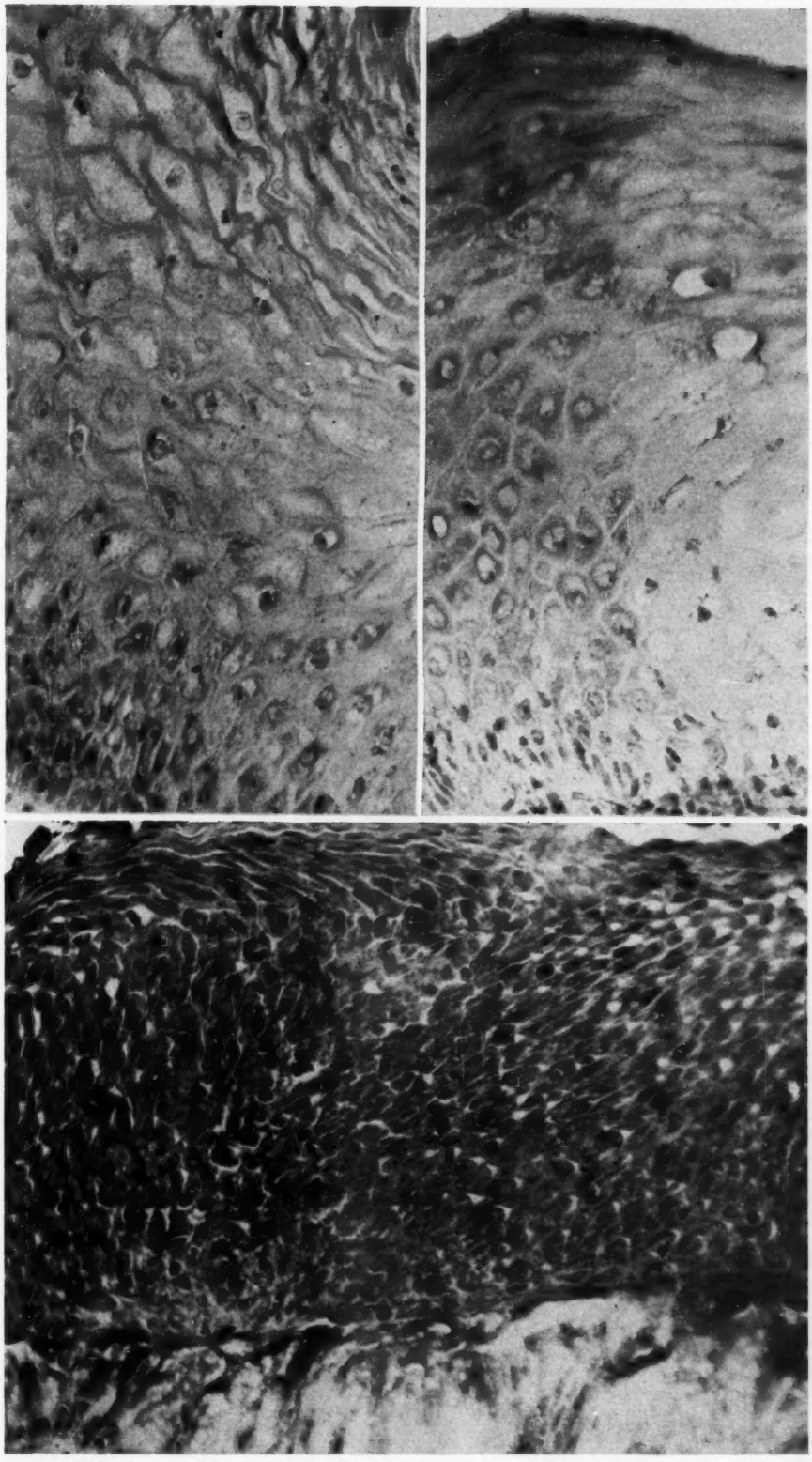


Fig. 8.

Figs. 6-8.—*For legends see opposite page.*

marked reaction. Comparing malignant to normal areas in the same specimen, frozen sections revealed the former to be markedly positive, whereas in the two carcinomas in situ no appreciable difference was observed in the less sensitive paraffin sections. Invasive cancer had unequivocally the most intense NSE activity (Figs. 10 and 11).

Columnar epithelium: Paraffin sections showed slight to heavy reactions but varied from case to case and gland to gland; there were variations even in portions of single glands. This was equally true in surface columnar cells. Nuclei often were positive, representing as in squamous cells diffusion artifact. Distribution in the cytoplasm was mainly luminal but often diffuse, and rarely subnuclear. Cell membranes were markedly positive. Negative glands were not infrequent. Frozen sections had similar localization but presented a heavier reaction, more discrete precipitate, negative nuclei. No cyclic menstrual trend was observed. Although several premenopausal cervices had over-all heavy gland reaction, none of the menopausal ones disclosed more than slight activity.

Acid Phosphatase.—In most histochemical reactions or stains for specific substances our efforts were directed to control the conditions so as to obtain a minimal reaction in poorly reacting tissue rather than attempting (as is more usual) to achieve a maximal response. ACP manifested the same gradient of activity in paraffin, fixed and unfixed frozen sections as nonspecific esterase. Seligman's method for paraffin and the modification for frozen sections produce a brown precipitate. The end product with Burton's technique is black.

Squamous epithelium: Paraffin sections subjected to the Seligman and Manheimer method were variable. Some were negative; some had slight activity. A few had quite strong reactions. Often, in large measure, this represented diffusion from underlying glands. The basal layer, particularly at the cell membrane, was most positive. The prickle-cell layer had fewer and smaller droplets. The granular layer displayed moderate activity. Inflammatory foci were associated with slightly increased reaction. The results with Burton's technique were similar. Intercellular bridges were quite prominent. In frozen sections there were the same over-all observations. The end point, however, was sharper. Although with Burton's method details occasionally appeared hazy, nonspecific reaction and diffusion were considerably less than with the other techniques. One slight difference in localization became apparent. With Burton's method ACP activity occurred mainly in the prickle and granular layers whereas with the other techniques the heaviest reaction was in the basal layer.

Menstrual cycle: There was no correlation with the menstrual cycle or menopause.

Benign changes: Definite increased activity was observed. In epidermoid hyperplasia, particularly, the prickle-cell layer had an intense reaction (Figs. 12 and 13*A*).

Squamous carcinoma: Both paraffin and frozen sections of untreated invasive cancer (Cases 2 and 3) revealed very marked activity throughout the malignant regions. Normal areas were almost negative (Fig. 19). In one case

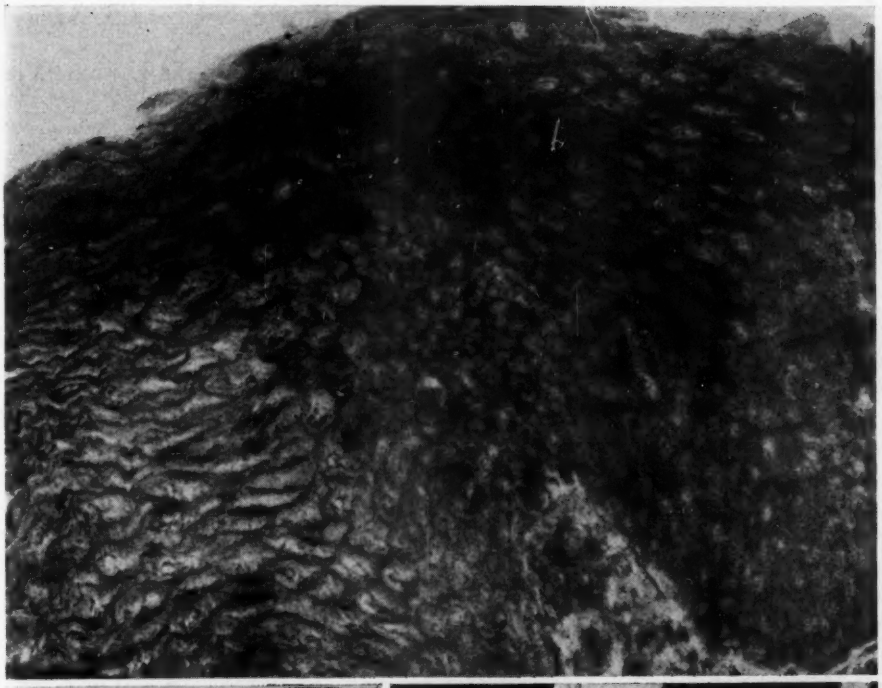
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Fig. 9.—Path. No. 55-2175. Nonspecific esterase in leukoparakeratosis. Frozen section. Abrupt increase occurs in the leukoparakeratotic area (right). Droplets tend to cluster about the cell membranes. (×550; reduced ¼.)

Fig. 10.—Hospital No. 37,291. Nonspecific esterase in invasive carcinoma. Frozen section. The patient was in the fourth month of gestation at the time of operation. Normal squamous epithelium, slightly positive, is seen at the top. Invading malignant epithelium, many foci of which have intense activity, is seen in the lower half of the illustration. (×19; reduced ¼.) (Courtesy Pondville Hospital.)

Fig. 11.—Hospital No. 37,291. High-power view of lower left corner, Fig. 10. The intensely positive malignant epithelium, now oriented at the top, is in striking contrast to the normal epithelium of the portio. (×115; reduced ¼.) (Courtesy Pondville Hospital.)

Fig. 9.



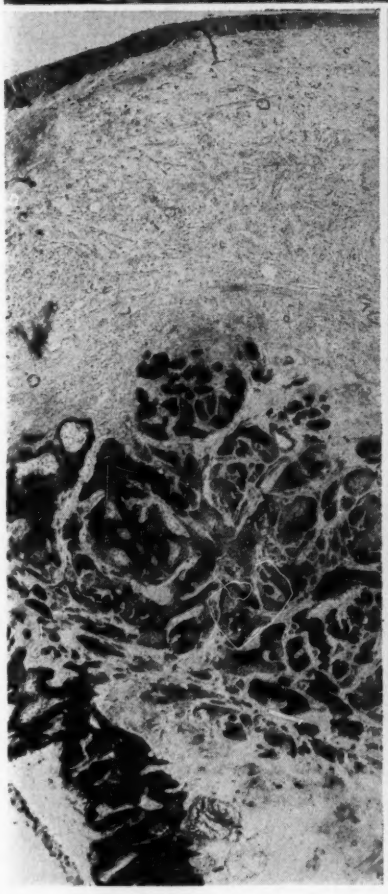


Fig. 10.



Fig. 11.

Figs. 9-11.—*For legends see opposite page.*

of carcinoma in situ (Case 1) paraffin sections disclosed slight if any increased ACP (Fig. 18). Unfortunately there were no frozen sections through a malignant area in this case. The other example of carcinoma in situ (Case 4) had decidedly increased ACP activity (Figs. 14 and 15). Cell nests of irradiated cancer, in which there was no viable tumor, reacted very lightly.

Summary of squamous changes: In a total of 17 normals (paraffin and frozen sections) all presented at best only slight ACP activity. In the groups with benign changes 2 of 4 had moderate reactions. In untreated cancer one had slight, one moderate, and two marked quantities of ACP. Except for one carcinoma in situ, all had 2 to 3 plus activity in the malignant areas. Unlike nonspecific esterase where both carcinomas in situ uniformly had somewhat less activity than the invasive lesions, amounts of ACP were variable. Thus there is a gradient of ACP activity. The reaction is slight in all normals. Some increase was noted in benign changes and a definite trend to consistently heavier reaction in malignant squamous epithelium could be detected.

Columnar epithelium: Reaction and localization were variable in the manner described for nonspecific esterase. Secretion was positive. Adenomatous hyperplasia reacted minimally. Frozen sections had the same over-all localization as paraffin sections except for an absence of nuclear reaction. Comments regarding squamous epithelium with Burton's technique are equally applicable here. A tendency to diminished activity was noted in menopausal cases.

Glucuronidase.—This very delicate enzyme is rapidly destroyed by heat and prolonged fixation. Even 10 minutes in cold 10 per cent formalin diminished activity in the normal cervical tissue to the barest minimum. Unfixed sections had greater activity but no benign cervical epithelium presented more than a slight reaction.

Squamous epithelium: Small, faint blue granules were noted especially at the periphery of the cytoplasm clustering about the cell membrane of the basal and prickle-cell layers. Scant if any precipitate could be found elsewhere although the granular layer had few droplets in patchy distribution. All control slides were negative. Altering incubation time, concentration of substrate or diazo dye, and other variables, did not increase the reaction. Often slides were entirely negative. In this regard glucuronidase was unique.

Menstrual cycle: The reaction was too slight to detect any cyclic or menopausal correlation.

Benign changes: The reaction was scant and not appreciably different from the normal.

Squamous carcinoma: Definite increased beta glucuronidase activity was found in each case. The most marked reaction, though not as intense as nonspecific esterase or acid phosphatase occurred in Case 3 (Fig. 20). Nevertheless, its presence was in striking contrast to the almost negative response elicited in normal and benign sections. A slight reaction occurred in nests of the irradiated lesion without viable cancer. A second case with prior irradiation,

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Fig. 12.—Path. No. 55-2236. Acid phosphatase. Burton's technique. Abrupt increase occurs in epidermoid hyperplasia (left). Frozen section. (×75; reduced ¼.)

Fig. 13*A*.—Path. No. 55-2236. High-power view of area with epidermoid hyperplasia. Reaction is intense. (×262; reduced ¼.)

Fig. 13*B*.—Path. No. 55-2175. Acid phosphatase in normal portio epithelium. Maximal concentration occurs in the prickle-cell layer (Malpighian) with Burton's technique. As with nonspecific esterase, droplets cluster about cell membrane. (×370; reduced ¼.)

Fig. 14.—Path. No. 55-3216. Carcinoma in situ reacted for acid phosphatase. The transition between the relatively light normal area (right) and the dark malignant zone is not unlike the change in Fig. 12. Burton's technique. Frozen section. (×75; reduced ¼.)

Fig. 15.—Path. No. 55-3216. Higher-power view of malignant area in preceding case. (×270; reduced ¼.)

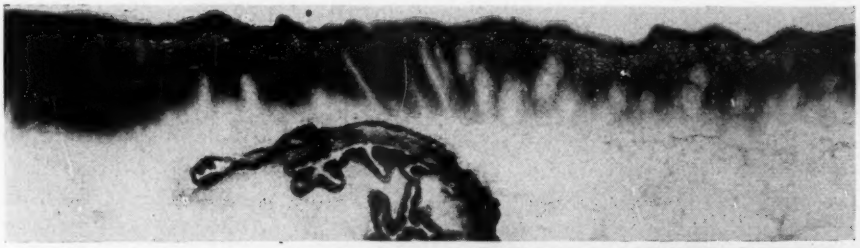


Fig. 12.

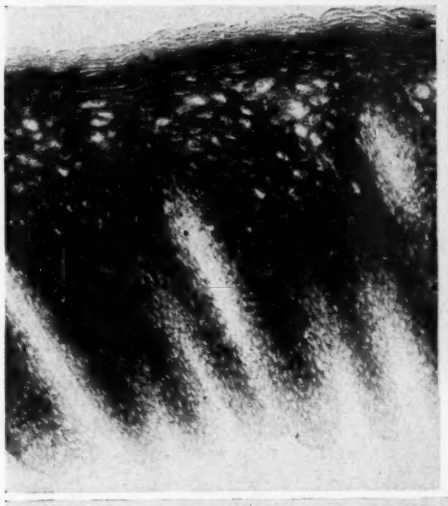


Fig. 13*A*.

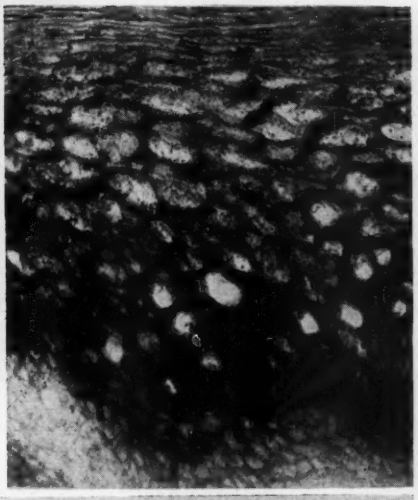


Fig. 13*B*.



Fig. 14.

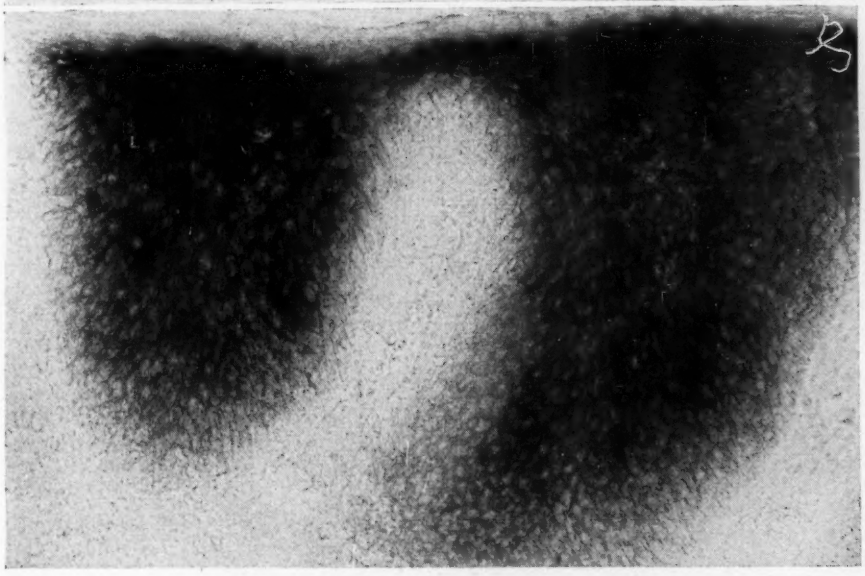


Fig. 15.

Figs. 12-15.—*For legends see opposite page.*

with some viable tumor, was moderately positive. Diffusion about the glands was sufficient to interfere with interpretation regarding the reaction of viable tumor cells.

Summary of squamous changes: Despite the small number of cases it was evident that there occurred an increased amount of glucuronidase in squamous carcinoma which seemed to be specific for malignancy.

It is important to stress that tissue be obtained fresh and be frozen at once because the human cervix has relatively little glucuronidase and because the enzyme is very sensitive. The section should not be permitted to dry more than a few minutes before being placed in the incubating medium; if preliminary fixation is elected, it should not be prolonged more than 10 to 15 minutes.

Columnar epithelium: Considerable diffusion was observed. A 2 per cent saline solution improved the situation only slightly. The degree of reaction varied from trace to 2 plus. Occasional nests of inflammatory cells were noted to have a reaction greater than that of the surrounding stroma. This was never greater than 1 plus. Because of the diffusion, specific and detailed description of the localization was impossible. Distal cytoplasmic concentration in the columnar cells seemed to be less prominent than with the esterases. Because of the factors previously noted cyclic and menopausal correlation could not be properly ascertained.

Substances and Reactions Not Significant in Carcinoma of the Cervix

Such constituents are lipids, sulfhydryl-disulfide, alkaline phosphatase, and, possibly, phosphamidase.

Lipids.—The over-all intensity of staining was slight. In squamous epithelium a fine particulate precipitate appeared in all layers. The largest and most numerous droplets appeared in the basal layer. Clustering occurred at the cell membrane, particularly in the basal aspects of the cell. The cell membranes and intercellular bridges were positive. Minimal staining appeared in the granular layer. No correlation with either the menstrual cycle or the menopause was noted in squamous or columnar cells. Benign squamous epithelium as well as squamous carcinoma stained lightly. Irradiated nests of cancer were negative except for scattered droplets. The cytoplasm of columnar cells stained lightly and diffusely although occasionally a luminal distribution of the larger droplets was observed. The cell membranes were intensely positive.

Sulfhydryl-Disulfide.—Coalescing pale red-purple droplets in both nucleus and cytoplasm identified SH; a darker red-purple precipitate indicated SS groups. In squamous epithelium the cell membrane and intercellular bridges were sharply demarcated and positive. The latter were identifiable even in the basal layer. It is impossible to claim with conviction that SS groups were definitely isolated because their presence was recognized only by intensification of the SH preparation. This occurred particularly in the superficial layers. There were no cyclic menstrual or menopausal variations in either squamous

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Figs. 16-19.—All were paraffin sections reacted for acid phosphatase by the Seligman and Manheimer technique.

Fig. 16.—Path. No. 55-1407. Normal epithelium of the portio is minimally positive whereas a group of cells representing squamous metaplasia (right of center at bottom) appears strongly positive. This probably represents diffusion artifact from nearby intensely reacting glandular columnar epithelium. (×115; reduced ¼.)

Fig. 17.—Path. No. 55-1420. Artifactitious nuclear reaction in an endocervical gland. (×550; reduced ¼.)

Fig. 18.—Path. No. 55-2865. Junction of normal epithelium and carcinoma in situ. Minimal or no increase of acid phosphatase in malignant cells. Flare of dark stain is due to diffusion from an underlying gland. (×130; reduced ¼.)

Fig. 19.—Path. No. 55-1869. Invasive squamous carcinoma sharply demarcated from the normal epithelium by its intense reaction; the latter appears negative (×7.5; reduced ¼.)

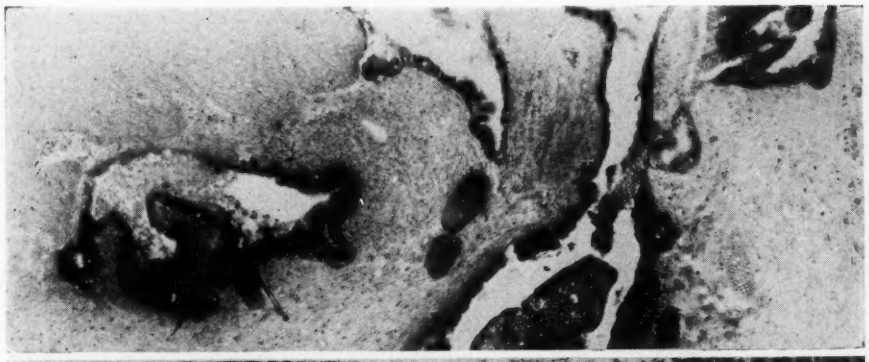


Fig. 16.

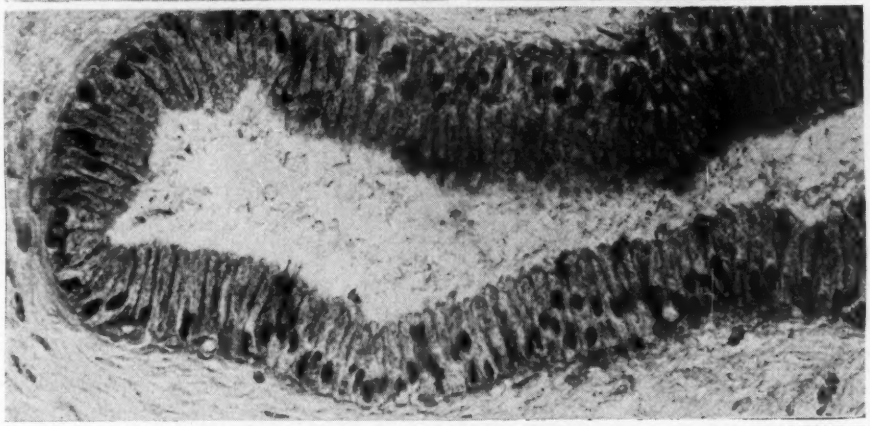


Fig. 17.

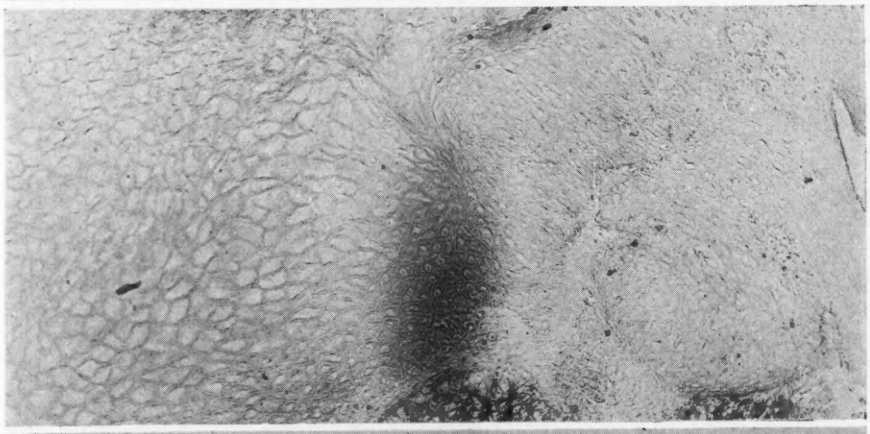


Fig. 18.

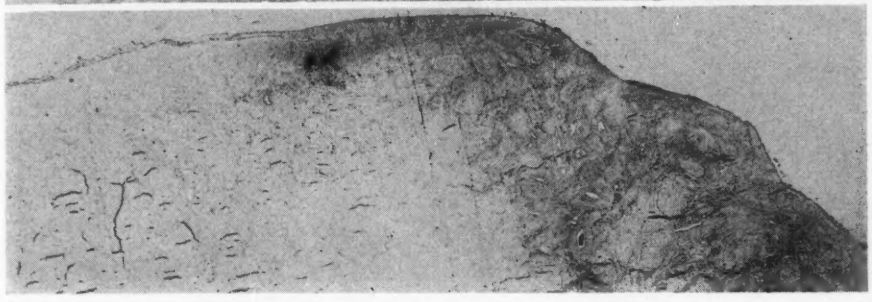


Fig. 19.

Figs. 16-19.—*For legends see opposite page.*

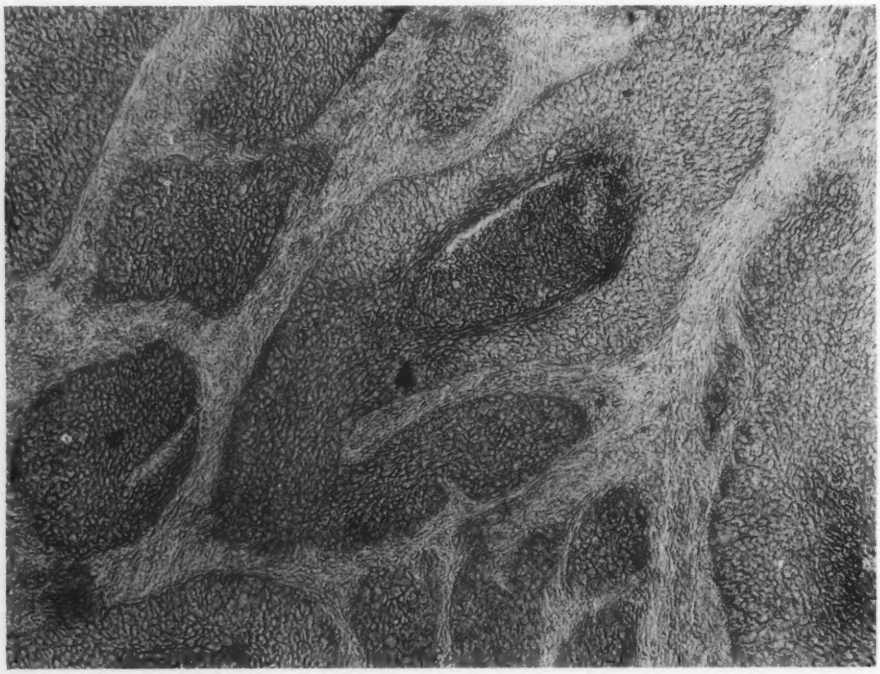


Fig. 20.—Hospital No. 37,291. Invasive squamous carcinoma of the cervix in pregnancy reacted for glucuronidase. Note clustering at cell membranes. Normal areas in this case as well as in benign cervices were almost negative (×130; reduced ¼.) (Courtesy Pondville Hospital.)

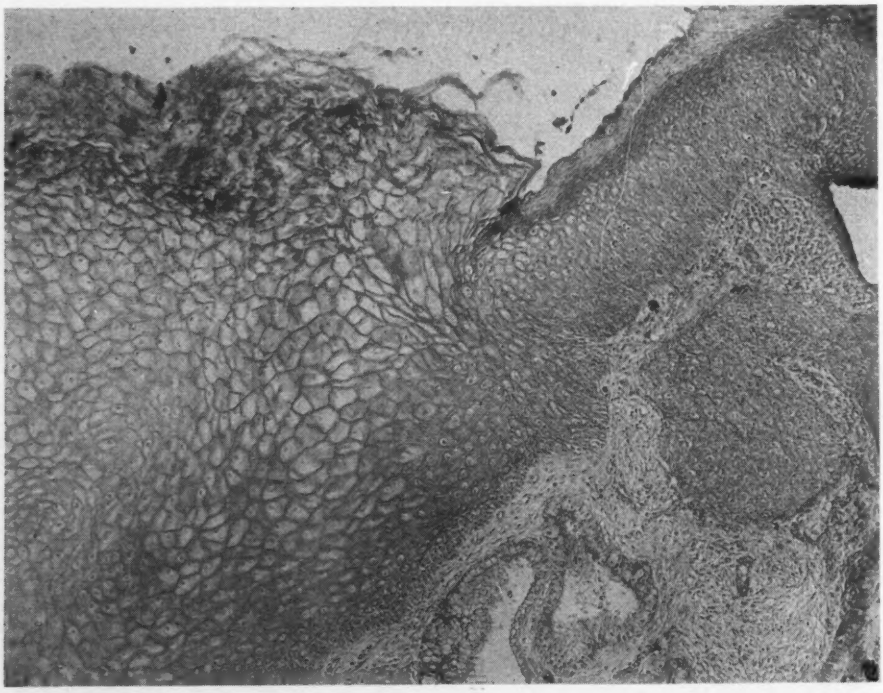
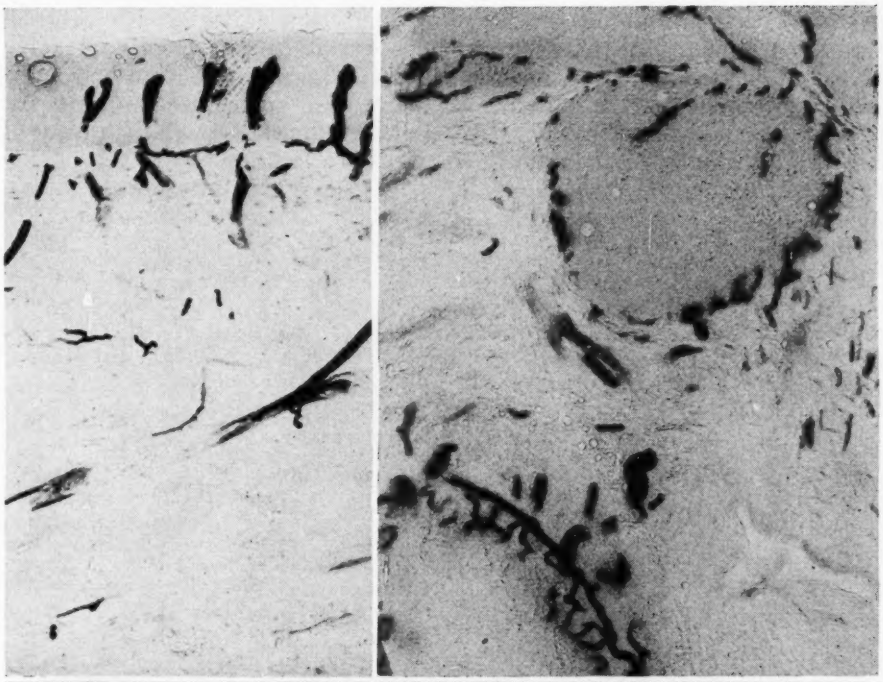


Fig. 21.—Path. No. 55-2865. Junction of carcinoma in situ with normal squamous epithelium reacted for sulfhydryl. Except for changes in morphology, little if any alteration in intensity could be appreciated. Disulfide appears mainly in keratinized zones whereas sulfhydryl occurs predominantly in the relatively immature layers. (×130; reduced ¼.)

Fig. 22. Fig. 23.



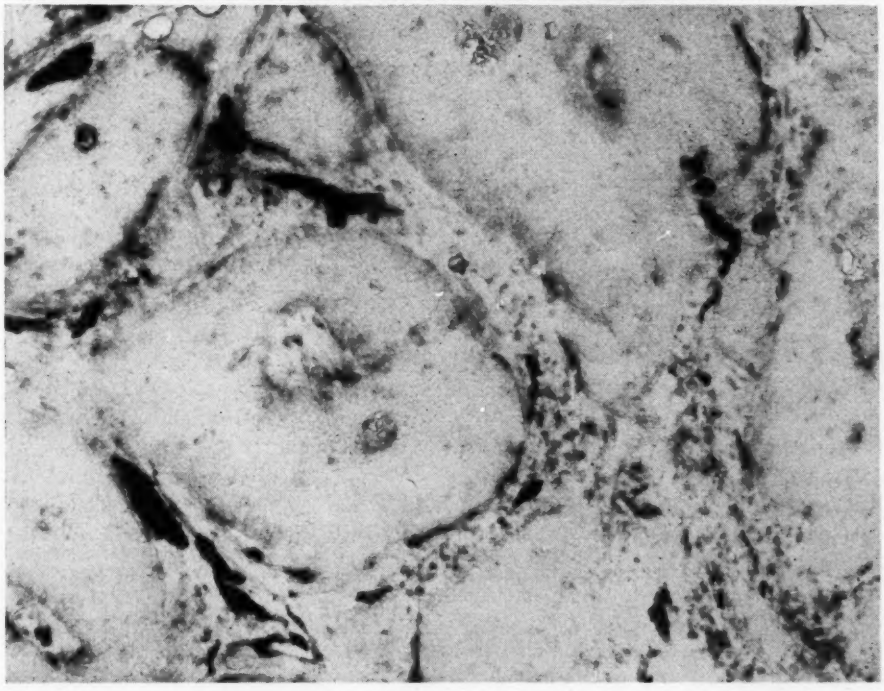


Fig. 24.

Figs. 22-24.—Alkaline phosphatase. Frozen sections. Squamous epithelium was negative in all cases. Note the striking pattern produced by intensely reacting vasculature.

Fig. 22.—Path. No. 55-2772. Normal portio. (×52; reduced ¼.)

Fig. 23.—Path. No. 55-3216. Carcinoma in situ. Invaded glands are outlined by the blood supply. (×52; reduced ¼.)

Fig. 24.—Hospital No. 37,291. Invasive squamous carcinoma showing nests of malignant cells. Note the intense reaction in endothelium of surrounding vessels which show slight diffusion to the periphery of tumor. (×90; reduced ¼.) (Courtesy Pondville Hospital.)

or columnar cells. Neither were there significant alterations in benign or malignant epithelium other than the normal morphologic ones (Fig. 21). Abnormal keratoses stained heavily, however, especially for SS groups. In irradiated carcinoma the hyalinized surface was very strongly positive for SH. Nests of irradiated squamous cells revealed minimal SH and SS. Columnar cells were moderately positive. Nuclei, cell and basement membranes were positive and generally sharply delineated. Most of the cytoplasmic droplets were located at the brush border.

Fig. 25.

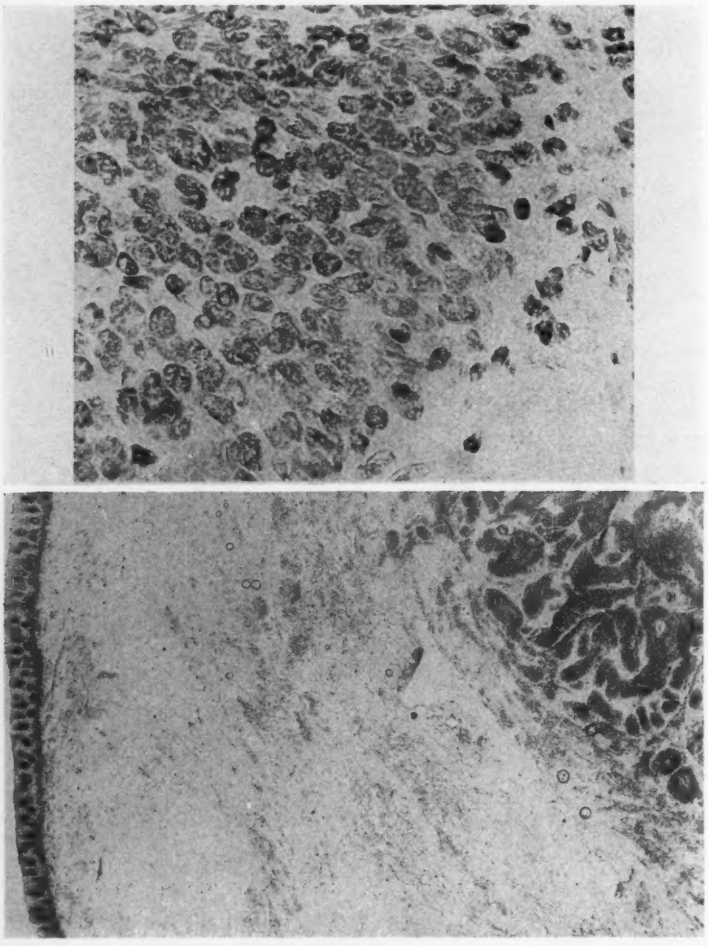


Fig. 26.

Figs. 25 and 26.—Invasive carcinoma reacted for phosphamidase. Frozen section.

Fig. 25.—High power to show nuclear details in a nest of malignant cells. (×470; reduced ¼.)

Fig. 26.—Hospital No. 37,291. Portion of the normal squamous epithelium, the nuclei of which appear darker than those of the malignant cells. (×19; reduced ¼.) (Courtesy of Pondville Hospital.)

Alkaline Phosphatase.—The squamous epithelium in all cases, normal and pathologic, revealed no ALP activity. Capillary endothelium reacted markedly; occasionally because of diffusion from these very positive sites, adjacent squamous epithelium suggested artifactitious activity. (See Figs. 22, 23, 24.) In columnar epithelium, localization and variability were reminiscent of the other esterases. Nuclei were negative. Although no cyclic correlation with

the menses was found, menopausal cases had an increased number of negative glands as well as an over-all lighter reaction than the premenopausal group.

Phosphamidase.—Paraffin sections were negative. In frozen sections of all 10 cases localization was restricted to the nuclei of squamous and columnar epithelium, the chromatin granules being unusually well outlined by the precipitate (Fig. 25). Nonspecific extracellular precipitate did not occur. Although strikingly uniform in normal cases, the possibility that nuclear localization was an artifact cannot be entirely dismissed. The basal layer of squamous epithelium was always strongly positive. The reaction was less consistent in the overlying layers, but not infrequently reached the surface (Fig. 26). In the superficial layers some nuclei were pale and some entirely negative. For the most part the surface was clear. Unfixed slides were lighter and had better detail than those with preliminary fixation. In the latter groups the nuclei more often than not appeared solidly black. No cyclic menstrual or menopausal trends were noted. In the one case with benign squamous epithelium (epidermoid hyperplasia) no deviation from the normal occurred. A variable response was found in squamous carcinoma. Some cases were heavier, unchanged, or lighter than normal (Fig. 26). In only one case were the normal areas negative and the malignant cells positive. Irradiated nonviable malignant cells were positive and presented the usual morphologic alterations. In columnar epithelium the reaction was restricted to the nuclei. Most were strongly positive. Completely negative glands were rare. Some had areas which were positive and others negative. Chronic inflammatory cells were coarsely stippled throughout the cell.

Comment

A complete review of the literature pertaining to the histochemical study of cancer as well as details of technique is to be covered at length in a subsequent paper. Here we will refer quite briefly to the pertinent literature and evaluate the significance, if any, of our findings with respect to the human cervix uteri. Relatively few histochemical studies have been done on the cervix. In the discussion to follow, reference will be made to material other than cervical on which histochemical techniques have been applied in order to elucidate present concepts of the significance of histochemical reactions in tissue metabolism.

Glycogen-Mucin.—Mucin is not present in cervical squamous epithelium. For a complete discussion the reader is referred to a recent article by Wheeler.[69] One of the early methods of demonstrating a difference between normal and malignant tissue was the Schiller test. When iodine is applied to the portio of the cervix, abnormal areas, lacking glycogen, remain unstained. In 1936 Schiller[62] discussed the diagnosis in a case of early carcinoma of the cervix. In 1949 McManus and Findley,[44] utilizing the PAS technique first described in 1946 by McManus,[43] reported the absence of glycogen from active squamous epithelium in carcinoma in situ of the cervix. This has been confirmed by others.[30, 36] It was noted that in malignant lesions glycogen was present only in mature cells.

Neither the Schiller test observed grossly nor the histochemical PAS reaction microscopically shows changes specific for malignancy. Alterations such as anaplasia, leukoparakeratosis, prickle-cell hyperplasia (basal-cell hyperplasia) as well as undifferentiated cancer have diminished or no glycogen. Uniformly our findings revealed absence of glycogen in immature cells whether they occurred in normal epithelium (basal layer), in hyperplasia, or in carcinoma. Where malignant cells showed morphologic evidence of maturity, glycogen was present (Figs. 2 to 5).

Ribonucleic-Desoxyribonucleic Acids.—Accurate quantification of nucleic acids cannot be done by histochemical methods. Microabsorption spectroscopy

is a relatively new technique so employed.[45] Leuchtenberger[38, 39] noted that deviating patterns in malignant tissue are not specific. Because nucleic acids are closely identified with chromatin, ultimately proper interpretation of morphologic alteration of the latter will be influenced by correlation with chemical changes in the former. As yet the nature of the linkages in nucleic acids is uncertain. Certainly further elucidation of the composition is necessary before differences between normal and abnormal tissues can be intelligently discussed.[30]

DNA is present mainly in chromatin; no cell nucleus has been found to be without DNA.[30] Early studies showing increased DNA in malignancy have not been reliably substantiated by newer techniques. It appears that the DNA of a resting cell is constant for the species.[30, 48] An increase of DNA in malignancy probably represents only what would be expected from mitosis.[30, 38]

There are no reliable data pertaining to quantitative determination of RNA in single cells. In normal skin Brachet[5] observed a decreasing gradient from the basal layer to the stratum corneum. Several studies have appeared in which histochemical techniques have been applied to both normal and malignant tissues.[45, 57, 58, 63] No modern report pertaining specifically to RNA in cervical carcinoma has been found. In other organs, results tend to show increased nucleoprotein in cancer.* Studies of benign growing tissue often have been inconsistent regarding RNA and DNA.[68]

Our data revealed no histochemical alterations of DNA; on the other hand RNA seemed variably to be increased in *immature* tissue whether benign or malignant. In normal portio epithelium the heaviest concentration occurred in the basal layer. Leukoparakeratosis, anaplasia, and cancer were characterized by large amounts of cytoplasmic RNA in the immature areas. Thus an increase, while not specific for malignancy, occurs to a greater degree in rapidly growing areas (Figs. 6 to 8).

Nonspecific Esterase.—Because of the possibility that there may be more than one type of NSE, it is not surprising that histochemical reactions may vary. Cohen and Seligman[8] found that, except for thyroid lesions, cancers had less NSE activity than the homologous normal tissue, thus agreeing with the postulate that in general malignant tumors have diminished enzyme activity.[25] Nuclear staining was not observed. Our results utilizing the same azo dye method were at striking variance with these findings. Untreated malignant lesions of the cervix displayed markedly increased NSE. This trend was present in paraffin as well as frozen sections. Furthermore, in certain instances benign changes had a greater reaction than any of the normal group (Figs. 9 to 11). Unpublished data of McKay's from our laboratory show that malignant lesions of the endometrium have greater activity of NSE than normal endometrium.

Acid Phosphatase.—Gomori's[21] method for this enzyme described in 1941 has been superseded by the simpler and more precise azo dye technique adapted by Seligman and Manheimer.[59] In its original form it had been applied to alkaline phosphatase.[46]

Although ACP is present in almost all animal cells the normal prostate is particularly well supplied with this enzyme.[35] In 1936 Gutman[26] applied this finding to the study of prostate carcinoma. His classic investigations resulted in the biochemical acid phosphatase test for metastatic carcinoma of the prostate.[27-29] ACP is the classic example of how a neoplasm may exhibit the same chemical specificity as the homologous tissue of origin. Actually, however, malignant prostatic tissue often has less than normal histochemical activity for this enzyme.[29, 37, 67]

*After completion of this report, findings of increased size as well as numbers of nucleoli in human ovarian papillary serous tumors were described by Taylor, AM. J. OBST. & GYNEC. 70: 753, 1955.

The actual role of all the phosphatases in cellular metabolism, as with so many other enzymes, is poorly understood and will not be commented on. The problem of substrate specificity, the question whether acid phosphatases of different tissues (or even in a single cell) are the same enzyme, and the complex problem of responses to activators and inhibitors likewise cannot be considered here.

Although articles have appeared[11, 20] describing histochemical localization of ACP in the female genital tract none could be found describing accurate localization in cervical cancer. On the whole most reports reveal increased ACP activity in malignant tumors. This has been documented in a heterogeneous group of malignancies including those of colon, stomach, breast, bronchus, skin, prostate, bladder, and bone.[21, 23, 30, 37, 49, 72] Similar results were obtained in epithelial tumors of mice.[73] Our data, showing a variable increase in squamous cancer of the cervix, as well as in benign lesions, served in addition to emphasize what is often overlooked in many reports, namely, that *there was no specific relationship to malignancy per se.* All of the normals had at best only slight activity. In the group with benign changes one half had moderate activity. All frozen sections in the malignant cases reacted more intensely than the normals (Figs. 12 to 19). The variable response based on one malignant case showing only slight activity in paraffin sections might well be due to limitations of the method as to inherent factors other than just growth.

Of considerable interest was the finding of nuclear reaction with both nonspecific esterase and acid phosphatase. At the present time this is considered to be artifact since the consensus is that most esterases are located in the cytoplasm. Although it had been felt that azo dye methods did not show nuclear reaction,[12, 24] workers[12, 65] recently have reported it in acetone-fixed paraffin-embedded sections. Fig. 17 illustrates nuclear staining with the Seligman and Manheimer technique. Nuclei were negative in frozen sections.

Beta Glucuronidase.—This enzyme, specific for the beta glycoside linkages of glucuronides, has attracted considerable interest in the past 10 years.[55] Its function in normal tissue is unknown. It probably is of importance in the conjugation and hydrolysis of steroids; a relationship to estrogen metabolism has been implicated.[13, 14] Its possible role in the cellular proliferation is especially intriguing.[40]

In 1947 Fishman[15] reported that homogenates of various malignant tissues have greater than normal quantities of beta glucuronidase. More recently, in collaboration with Kasdon, Homburger, and others, he[16, 33, 34] assayed vaginal fluid in patients with carcinoma of the cervix. Significantly increased beta glucuronidase activity was noted. A considerable number of normal postmenopausal women also had high activity, however. Possible sources of enzyme other than malignancy could have been leukocytes and vaginal mucosa.[33] Lorincz[41] attributes the activity of beta glucuronidase in vaginal secretion to bacterial action and cellular debris as well as to cancer cells. In general his studies of vulvar, vaginal, and cervical malignancies confirmed Fishman's findings. Boyland[4] found high urinary glucuronidase in patients with bladder carcinoma. Increased activity in the malignant tissue itself was noted. Wied[70] reported similar results in female genital malignancies in assays of blood, urine, and vaginal secretions. Endometrial carcinoma has not been shown biochemically to have elevated glucuronidase activity.[41, 70]

In contrast to the relatively large volume of biochemical reports devoted to glucuronidase assays there is very little published material concerning histochemical localization. Available methods for a long while proved unsatisfactory in practice because of difficulties in obtaining a stable, easily prepared substrate for a reaction which would be both reliable and reproducible. Nevertheless some data showing localization in cancer appeared in 1949.[7, 60] In 1954

Seligman[61] reported the preparation of a substrate for diazo coupling which permitted fairly satisfactory localization of glucuronidase. In our hands this technique disclosed minimal beta glucuronidase in the normal human cervix. Particularly scant was the reaction in the squamous epithelium of the portio. Benign squamous epithelium reacted very faintly. In comparison untreated malignant squamous epithelium showed marked activity (Fig. 20). Individual sections however, varied in intensity, probably due to technical factors.* Thus beta glucuronidase may be specifically increased in squamous cancer of the cervix. In so far as some activity is present in normal cells, there must remain, however, a gradient of activity from the normal to the malignant squamous epithelium.

Lipids.—Regarding malignancy suffice it to say that no significant histochemical reports have appeared and our findings indicate no specific correlation with any lesions of the cervix in this series.

Sulfhydryl-Disulfide.—Protein bound SH and SS groups have provided major interest, particularly as related to keratinization. The pertinent literature has been carefully reviewed by Wheeler.[69] Whereas the keratinized zone of squamous epithelium contains some SH as well as a variable amount of SS, the Malpighian layer has mainly SH.[3] The chemistry of keratinization is complex and is not entirely understood. The chemical distinction between soft and hard keratin on a basis of SH in layers just under the keratinized zone has yet to be confirmed. It is known that these groups are important not only in keratinization but also in enzyme metabolism, cell division, and growth. There is very scant published experience referring to the role of SH and SS groups in cancer. Wingo and Foraker[71] in 1954 studied basal-cell tumors and epidermoid carcinomas of the skin for SH and SS. SH was distributed in the young growing zones and varied inversely with SS localization which was predominantly in the keratinized areas. The same workers[17] later reported a study of squamous-cell carcinoma of the cervix (biopsy material). SS was found wherever keratinization occurred, on the surface and in epithelial pearls, whereas SH was concentrated in growing zones in both normal and malignant cases. The authors concluded that SH and SS localization offered no change specific for cancer. Our results confirmed this (Fig. 21).

Alkaline Phosphatase.—Present knowledge of the role played by ALP in metabolism is incomplete. It is known that ALP liberates inorganic phosphates from mononucleotide, ribonucleic acid, and depolymerized DNA. As with acid phosphatase, it is not yet clear whether these activities are the properties of one or more enzymes. Both ALP and ACP are probably of great importance at the site of molecular transfer across cell membranes. The relationship to glycogen metabolism, calcification, and ossification has not been clarified. A possible connection with malignant growth has been investigated by both histochemical and biochemical techniques.

Franseen and McLean[18] in 1935 were the first to demonstrate high ALP content in neoplastic tissue (oesteogenic sarcoma) and blood plasma. Increased activity has been found in malignancies of the liver,[25, 30] hydatid moles,[56] ovarian carcinomas,[51] teratomas and embryonal carcinomas of the testis.[23, 30, 66] Atkinson and Gusberg[1] noted lower ALP in undifferentiated than in well-differentiated carcinomas of the endometrium. Moschino,[50] on the other hand, reported an inverse relationship of ALP activity to differentiation in adenocarcinoma of the endometrium. Using Gomori's method, Kabat and Furth[32] in 1941 observed minimal ALP in carcinoma of the breast. Drennen,[9] however, noted a gradient of activity; the greater the distance from the peripheral blood supply the less the activity. The author explained the increased reaction at the periphery of the tumor on a basis of blood supply. It now seems likely

*The number of slides in the incubating medium was a controlling factor in the intensity of reaction. Two slides close together reacted faintly whereas one by itself would react more intensely.

that because endothelium of blood vessels has marked enzyme activity, diffusion to adjacent structures caused confusion in interpretation. That this may happen with even the more precise azo dye methods can be seen in Fig. 24. Increased ALP actively described in healing wounds[19] deserves equal caution in interpretation.

Much of the histochemical work reported has been with Gomori's calcium phosphate technique. As with ACP and NSE the newer azo dye methods are more satisfactory in localizing ALP. In 1944 Menten, Junge, and Green[46] devised the coupling azo dye reaction specifically for ALP. The basic principle of this reaction consists of the hydrolysis of a monoaryl phosphate whereby the freed naphthol reacts at once with the diazotized amine dye producing an insoluble colored precipitate at the exact site of enzyme activity. It is from this ingenious procedure that subsequent modifications for the same and other enzymes arose.[42, 52, 59, 60, 61]

Utilizing the diazo coupling reaction in the investigation of cervical lesions we were unable to demonstrate ALP activity in portio squamous epithelium, normal or abnormal (Figs. 22-24). One must exercise extreme caution in ascribing a positive reaction in regions adjacent to intensely reacting structures, in the case of ALP, capillary endothelium. The slight increase in malignant cases appeared to be correlated with the increased vascularization.

Phosphamidase.—In 1948 Gomori[22] described a histochemical technique for phosphamidase, a specific monoesterase which hydrolyzes nitrogen-phosphate bonds. This enzyme was noted mainly in the cytoplasm but also appeared in the nuclei. Gomori observed an intense reaction in malignant epithelial tumors as well as in normal gray matter of the central nervous system. Application of this technique to lesions of the oral cavity confirmed the impression that certain epithelial cancer had high phosphamidase activity.[47] Results in both studies, however, were variable. Sporadic, inadequately documented reports have appeared in the foreign literature.[10, 53, 54]

The method has been critically reviewed by Pearse.[55] He concluded that it is not dependable, the substrate unstable, and the results variable. Whether or not phosphamidase is in fact a specific acid phosphatase remains uncertain.

In the cases we reacted for phosphamidase, paraffin sections were entirely negative. Of the normal groups all frozen sections disclosed uniformly positive results. Because of nuclear localization the question immediately arises whether or not this constitutes artifact. Nuclear localization may well be inaccurate. Nevertheless, because (1) nuclei uniformly were positive without extracellular precipitate, (2) controls (iodine treated) were negative, and (3) prolonged acetone-fixed paraffin-embedded tissue was negative, it seems reasonably certain that the reaction was due to the enzyme described by Gomori, whether or not this enzyme is a specific acid phosphatase.

Despite the fact that the present method is tedious and the substrate currently in use unsatisfactory, it is our feeling that this enzyme merits further careful study.

Summary

A total of 27 complete cervices including 5 squamous cancers were studied by a variety of histochemical procedures. Although definite conclusions are not possible at the present time, certain trends appeared evident.

Whereas glycogen is diminished in cervical cancer, ribonucleic acid, nonspecific esterase, and acid phosphatase are usually, but variably, increased. Glycogen is directly proportional but the others are indirectly proportional to the degree of morphologic differentiation.

Emerging as a finding of particular significance was the same trend in benign alterations of growth. That there is a greater variation in the concen-

tration of some constituents could be expected. Nonspecific esterase and glycogen are relatively consistent; ribonucleic acid and acid phosphatase are not. Rather than absolute differences, a gradient of activity could be recognized.

Sulfhydryl and disulfide, lipids, and alkaline phosphatase show no alteration in either benign or malignant growth.

The one available method for phosphamidase is not entirely satisfactory. Although there may be a significant alteration in phosphamidase content in malignant cervical epithelium, our findings were variable.

Of all the enzymes and cellular constituents thus far investigated, glucuronidase appears to be the only one in which increased histochemical activity may prove to be specific for malignant growth.

Conclusion

In the light of increasing experience, the oft-repeated postulate that histochemical activity is decreased in malignant tissue[25] appears to require clarification.

Within the bounds of chemical specificity for a given tissue, a cellular constituent appearing to be a function of maturation will be diminished in immature cells, whether benign or malignant. On the other hand, when a particular cellular constituent is a function of growth per se, one may expect cells from such growing tissue, whether benign or malignant, to have increased quantities of that constituent.

An analysis of the studies to date leads to the conclusion that histochemical activity, by and large, is specific for the tissue and the degree of differentiation but not for neoplasia as such. Thus there exist gradients of activity rather than absolute differences.

Slowly the chemical spectra of normal and malignant tissue are being clarified. As yet we have no specific and clear-cut distinction between the two. Continued critical application of present methods, as well as new techniques for chemical constituents which remain uninvestigated, may some day provide an answer for the alteration of growth unique to cancer.

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A CLINICOPATHOLOGIC STUDY OF 56 CASES SHOWING ATYPICAL EPITHELIAL CHANGES OF THE CERVIX UTERI

ARNOLD J. RAWSON, M.D., AND ROMAN KNOBLICH, M.D., NORFOLK, VA.

(From the Department of Pathology, Norfolk General Hospital)

THE concept of preinvasive intraepithelial squamous-cell carcinoma of the cervix uteri, which in many cases progresses to frank invasion, is now firmly established. There is less general agreement on the exact criteria for making a diagnosis of intraepithelial squamous-cell carcinoma of the cervix, but most students of the subject consider that intraepithelial carcinoma is present when the entire thickness of the cervical mucosa consists of atypical cells.[16, 14] Although the cytoplasm of these cells is frequently basophilic, the significant changes relate to the nuclei, which show variation in size and shape with a tendency to spindle form and increase in chromatin mass and in rate of cell division.[7] Because of variation in individual criteria, it has been suggested that recorded cases shown to have progressed to invasive carcinoma be used as type cases.[13] It is generally realized that many cases are seen in which there are found worrisome changes in the nuclei of the cervical epithelium, but in which the extent of the disease is insufficient for a diagnosis of intraepithelial carcinoma. This group is the most controversial and puzzling to clinician as well as to pathologist. A number of studies have been made of lesions of this type,[4, 6, 8, 13, 17] but it is felt that confusion still exists and further data would be of great value. For this reason the present study was undertaken. Some of the perplexing problems which have not as yet been fully answered deal with the relationship of these atypical changes to carcinoma, the significance of such changes in pregnancy, and the significance of such changes found in conjunction with Trichomonas infestation. Since nuclear abnormalities are the basis of the problems posed in these cases, we favor the use of the term "dyskaryosis," introduced by Papanicolaou,[11] for such lesions. This term is purely descriptive and avoids any etiological connotations. Histologic and cytologic descriptions of these lesions have been adequately recorded.[4, 13, 16]

Materials and Methods

Beginning in April, 1950, all cervical biopsies seen in the Department of Pathology at Norfolk General Hospital which showed nuclear abnormalities of the epithelium insufficient for a diagnosis of intraepithelial carcinoma were indexed as "dyskaryosis" and the patients were carefully followed. An attempt was made to have these patients followed by means of punch biopsy and smear at monthly intervals, but it was not always possible to obtain these specimens on schedule. All patients included in this series as determinate cases, however, were followed up to the present time or until definitive surgery

was performed. Both clinic and private cases are included in this series. The ratio of private to clinic cervical biopsies in our over-all material is about two to one. With few exceptions the private patients are white. About two-thirds of the clinic patients at this hospital are Negro.

Results

A. Etiology.—In an attempt to determine the significance of several possible etiological factors previously considered by other authors, the cases were subdivided into those associated with pregnancy or Trichomonas infestation, or unassociated with obvious disease. It will be noted in Table I that there were 16 cases in which the initial biopsy was taken during pregnancy, 3 in which Trichomonas infestation was present, and 37 in which neither of these factors was present at the time of the initial biopsy. A careful histologic comparison was made of the initial biopsies of all patients and no significant histologic differences sufficient for definitive differential diagnosis could be determined . In some of the cases of Trichomonas infestation, the prominent superficial changes consisting of giant nuclei and vacuolated cytoplasm described by Bechtold and Reicher[2] were found, but we are in agreement with these authors that in many cases the changes caused by Trichomonas infestation cannot be distinguished with certainty from other types of dyskaryosis.

TABLE I. SUMMARY OF ASSOCIATED CONDITIONS AND SUBSEQUENT COURSE IN 56 CASES OF DYSKARYOSIS

ASSOCIATED CONDITION	NO. OF CASES REGRESSING	NO. OF CASES ASSOCIATED WITH CARCINOMA	NO. OF CASES INDETERMINATE	TOTAL NO. OF CASES
Pregnant	10	3 (19%)	3	16
Nonpregnant	29*	5 (14%)	3	37
Trichomonas	3	0	0	3
Total	42	8	6	56

*Six of these cases showed no evidence of disease in the hysterectomy specimen.

B. Age, Race, Economic Status.—Reference to Table II shows the mean age at the time of the initial biopsy to be 34 years in the nonpregnant group whose lesions regressed, and 31 years in the pregnant group whose lesions regressed. Of particular interest is the close correlation of these figures notwithstanding the fact that the average age of pregnant patients in general is considerably younger (23 years in our clinic). The mean age of the nonpregnant patients in this series correlates well with the findings of others.[13] A similar correlation is seen in the observation that cases associated with carcinoma tend to occur at a mean age of one decade more than lesions which regress.[13]

TABLE II. AGE, RACE, AND ECONOMIC STATUS OF ALL PATIENTS WITH DYSKARYOSIS AT THE TIME OF INITIAL BIOPSY

ASSOCIATED CONDITION	COURSE	AGE (YEARS)		RACE		ECONOMIC STATUS	
		EXTREMES	MEAN	WHITE	NEGRO	PRIVATE	CLINIC
Pregnant	Regressed	23-39	31	5	5	3	7
Pregnant	Carcinoma	22-29	24	2	1	1	2
Nonpregnant	Regressed	23-56	34	18	11	17	12
Nonpregnant	Carcinoma	34-51	44	4	1	2	3
Trichomonas	Regressed	25-28	27	2	1	2	1

The extraordinarily low age of the group of patients with carcinoma following pregnancy is difficult to explain and may be a reflection of the small size of the group (3 cases).

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Fig. 1.

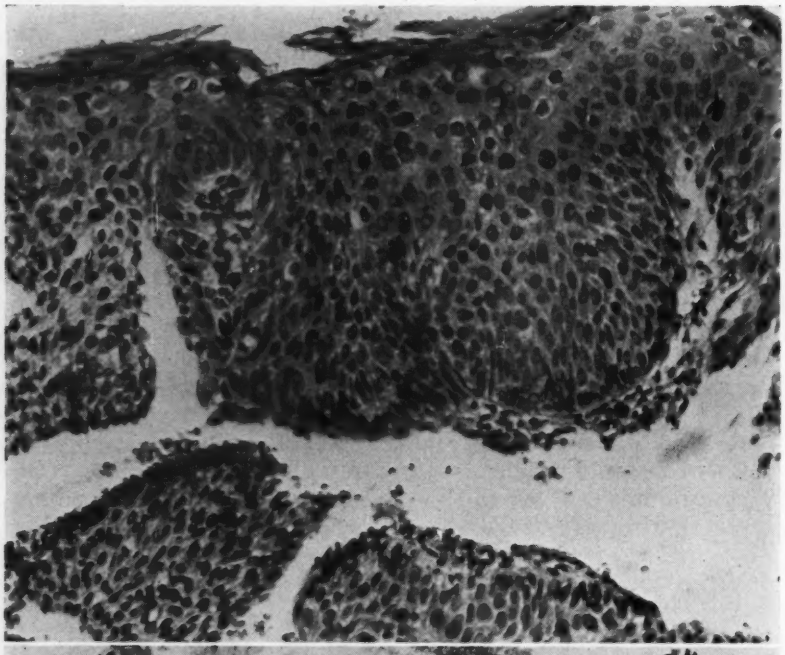


Fig. 2.

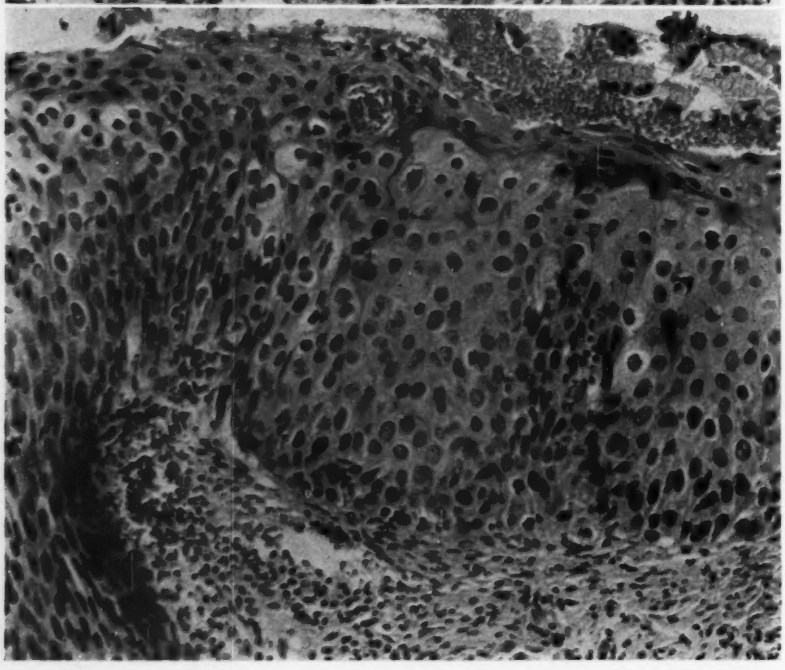


Fig. 1.—Biopsy of the cervix of a 27-year-old pregnant white woman. Similar changes were found in subsequent biopsies over a thirteen-month period. In the three years following the disappearance of the lesion, smears and biopsies have shown no evidence of disease.

Fig. 2.—Biopsy of the cervix of a 22-year-old pregnant white patient. Intraepithelial carcinoma was found in other areas of the same specimen, and early invasion was found in cone biopsy taken several days later.

Fig. 3.

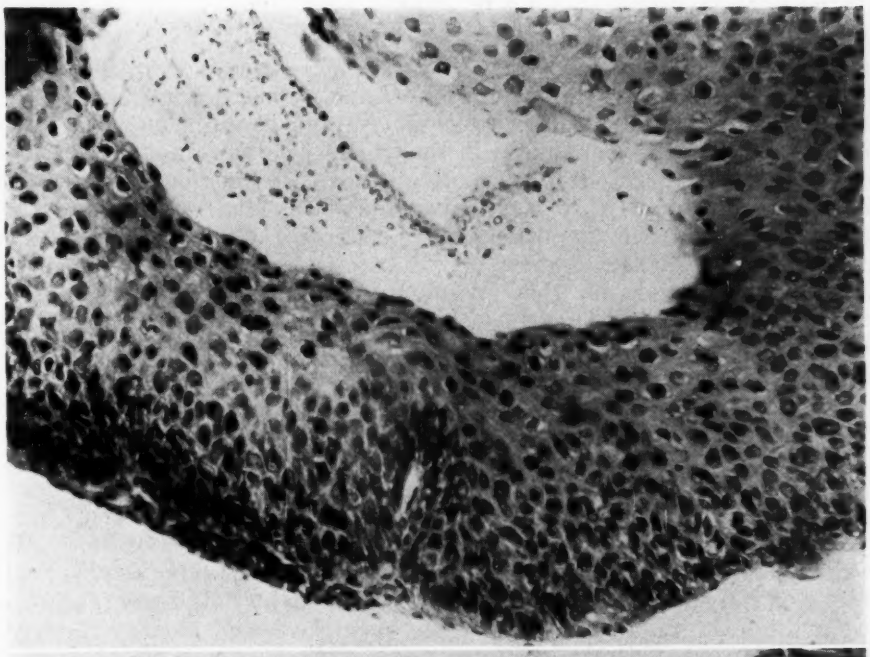


Fig. 4.

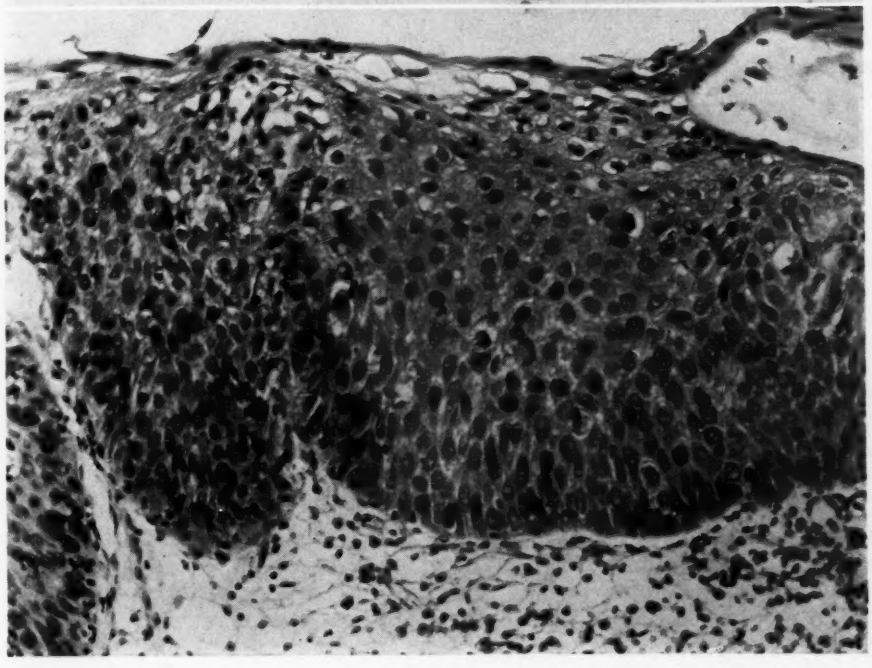


Fig. 3.—Biopsy of the cervix of a 36-year-old nonpregnant white woman without evidence of Trichomonas infestation. Repeat biopsy three months later showed no lesion. No subsequent recurrence.

Fig. 4.—Biopsy of the cervix of a 34-year-old nonpregnant Negro patient. Intraepithelial carcinoma was found by biopsy one month later. No invasion was found in the hysterectomy specimen.

The groups relating to race and economic status are too small to be conclusive. There is, however, no indication that Negroes or clinic patients are more apt to be affected.[13]

C. Clinical Course.—Reference to Table I will show that approximately one sixth of all patients were later found to have carcinoma. These cases were present in approximately equal proportion in the group who were pregnant at the time of the first biopsy and in the group who were not pregnant at the time of the first biopsy. In the small group of Trichomonas infestations no carcinomas were found. One of the carcinomas was frankly invasive, 2 showed early invasion, and all the others were intraepithelial. Careful histologic comparison of cases which regressed with cases which progressed to carcinoma showed that there were no good histologic criteria for predicting the future course of the lesion from the initial biopsy (Figs. 1-4). In this connection, it might be mentioned that dyskeratosis, which has been mentioned as an ominous sign,[1] was present as frequently and to the same degree in the cases which subsequently regressed as in those which were later found to be carcinomatous.

The time required for regression of dyskaryotic lesions is summarized in Table III. It will be noted that the majority of lesions had completely disappeared by six weeks after the initial biopsy, never to return during the follow-up period. A number of cases persisted longer, however. Most of these disappeared by four months, but one persisted as long as forty months. Instances of long-term persistence were found in both the pregnant and the nonpregnant groups. In all these cases, once the lesion cleared there was no tendency toward recurrence.

TABLE III. NUMBER OF MONTHS REQUIRED FOR DISAPPEARANCE OF DYSKARYOSIS IN CASES UNASSOCIATED WITH CARCINOMA

ASSOCIATED CONDITION	NUMBER OF CASES			
	LESS THAN 2 MONTHS	2-4 MONTHS	MORE THAN 4 MONTHS	NOT KNOWN
Pregnant	6	1	1*	2
Nonpregnant	17	6	2†	4

*13 months.
†8 months and 40 months, respectively.

Follow-up data on the cases which subsequently were shown to be carcinomatous are summarized in Table IV. It will be seen that 6 of the 8 cases were diagnosed as intraepithelial carcinoma within one month of the initial biopsy, and careful study of these cervices following hysterectomy showed that the dyskaryotic areas merged insensibly with those of carcinoma in situ and appeared to coexist with them. It is therefore a reasonable assumption that carcinoma was present in these cases at the time of the initial biopsy even though the latter showed only dyskaryotic change. One case did not reveal intraepithelial carcinoma until nineteen months after the initial diagnosis of dyskaryosis, in spite of repeated punch biopsies. A smear taken nine months after the original biopsy suggested carcinoma, however. Although there is a possibility of progressive change from dyskaryosis to intraepithelial carcinoma, it seems more likely that carcinoma might have been found earlier had a cone biopsy been done instead of punch biopsies. In the seventh case twenty-one months after the initial biopsy, the patient was found to have frankly invasive carcinoma. No stage of intraepithelial carcinoma was detected by repeated punch biopsies. This case lends itself to the same interpretations as the preceding one, and an intraepithelial stage might have been detected had a cone biopsy been done.

TABLE IV. TIME INTERVAL BETWEEN DIAGNOSIS OF DYSKARYOSIS AND DIAGNOSIS OF CARCINOMA

ASSOCIATED CONDITION	PATIENT	NUMBER OF MONTHS FROM INITIAL BIOPSY	
		CARCINOMA IN SITU	INVASIVE CARCINOMA
Pregnant	K. J.	Less than 1	Less than 1
	A. H.	Less than 1	24
	E. H.	Less than 1	--
Nonpregnant	A. M.	Less than 1	--
	L. W.	Less than 1	--
	M. B.	Less than 1	--
	J. B.	19*	--
	A. A.	None detected*	21

*See text.

Comment

Our data suggest that atypical changes of the cervical epithelium found in pregnancy do not differ significantly from those found in the nonpregnant state. The lesions appeared in comparable age groups, and histologically there was no obvious difference between the two groups (Figs. 1 and 3). The lesions which regressed disappeared as quickly in the nonpregnant as in the pregnant state. The same proportion of atypical changes later associated with carcinoma was found in the pregnant as in the nonpregnant group. It is our feeling that the factor of pregnancy should be disregarded in the diagnosis and evaluation of dyskaryotic lesions. Similar conclusions have been reached by others.[5, 10] While none of our cases associated with Trichomonas infestation subsequently was shown to be carcinomatous, it has been shown that Trichomonas and carcinoma may coexist and that the presence of significant atypical changes is an indication for further investigation along the same lines that would be followed were there no infestation with Trichomonas.[2] It is our feeling, therefore, that where dyskaryotic changes are found, further careful investigation should be pursued regardless of the presence of pregnancy, Trichomonas, or any other complicating factor.

We further feel that histologic criteria are inadequate to distinguish those cases which will subsequently regress from those which will subsequently be found to be carcinomatous,[6, 13] and that all cases must be carefully investigated. In agreement with the conclusions of others[6, 13, 16, 17] one of the most important points brought out by this study is that although dyskaryosis may in a few cases progress over a prolonged period into carcinoma, it is far more commonly a warning of the actual presence of carcinoma and coexists with it in about one sixth of all cases. It has been pointed out in this study and by others that dyskaryosis, where it coexists with carcinoma, merges gradually and imperceptibly into the latter lesion.[6, 7, 14] It has also been pointed out that dyskaryotic change commonly involves the portio vaginalis of the cervix,[7] whereas carcinoma in situ commonly involves the endocervical canal.[3, 7, 12, 15] For this reason the usual cervical punch biopsy may cut into an area of dyskaryosis and miss the coexisting carcinoma in situ. In view of the often patchy distribution of these lesions, study by random punch biopsies has been

found to be inadequate, and thorough investigation depends upon the employment of careful knife conization of the endocervix and portio vaginalis. Subsequent follow-up studies should always include smears.

If the possibility of coexisting carcinoma is excluded by means of the cone biopsy, the problem of treatment of dyskaryosis presents itself. In view of the fact that the vast majority of dyskaryotic changes unassociated with carcinoma will regress spontaneously, it is our feeling that no immediate treatment is indicated. We likewise feel that those few cases which might progress into carcinoma at a later date can easily be detected by follow-up smears done at frequent intervals. It has been amply demonstrated that dyskaryotic cells are easily detected in the smear,[9, 14] and the rare case in which dyskaryosis is seen to persist for more than four months should be carefully reinvestigated.

The results of this study shed no definite light upon the nature of dyskaryosis. We feel unable to express any opinion regarding the similarity of the disease processes found respectively associated and unassociated with carcinoma; nor are we willing to speculate upon whether these changes are precancerous or merely reactive changes often seen in the presence of a carcinoma.

Summary

The course of 56 cases showing nuclear atypicalities of the cervical mucosa has been reviewed.

About one sixth of these lesions were found subsequently to be associated with carcinoma; the remainder eventually disappeared completely.

Histologic criteria were inadequate for prediction of the future course.

No significant differences were found between lesions detected respectively in the pregnant and nonpregnant states.

It is suggested that nuclear atypicalities of the cervical mucosa be promptly investigated by cone biopsy, and that the cases showing no evidence of carcinoma after examination of the cone be followed by smears.

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MULTIPLE PRIMARY MALIGNANT TUMORS INVOLVING THE FEMALE GENITAL TRACT

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THE occurrence of multiple primary malignant neoplasms in a single individual seems to be regarded by many physicians as an extremely unusual event of questionable significance. That this is not the case is amply attested by the surprisingly long bibliography on the subject. For example, Warren and Gates[12] consulted 430 different papers in the preparation of their comprehensive survey of 1932, and many more reports have appeared since that time.

In their survey of the literature published in 1932, Warren and Gates presented 1,259 cases of multiple primary malignant neoplasms, including 40 cases of their own encountered in the course of 1,078 autopsies done on cancer cases. In 1944, Warren and Ehrenreich[11] presented, as a continuation of this series, a further 194 cases occurring in 2,829 autopsies on cancer patients, making the total incidence for their institution 234 cases in 3,907 cancer autopsies. In the second series the incidence of multiple primary cancers was 6 per cent in all deaths from cancer, compared with 3.7 per cent in the first series. The writers attribute this rise in incidence to two factors, an increased awareness of the possibility of multiple primary cancers, and the increased number of biopsies of skin cancers before treatment, together with the routine histologic examination of all tumors excised.

Slaughter,[8] in a collective review in 1944, presented 1,868 cases including 40 newly reported, an incidence of 3.9 per cent. However, 749 (40 per cent) of the cases he discussed were multiple lesions of the same organ, and 269 (14.4 per cent) were multiple lesions of paired organs, both situations in which the primary nature of both neoplasms is often difficult to accept.

The cases reported by these writers were all encountered at autopsies and of course do not include patients who had been successfully treated for cancer. Moreover, multiple cancers of the same organ, especially the skin, comprised a large percentage of the cases. The numbers of cases involving the female genital tract were relatively few, Warren and Gates' survey including 103, of which 10 were double primary lesions of the Fallopian tubes and 7 were double primary lesions of the uterine fundus, both situations in which acceptance of the diagnosis of double primary cancer is exceptionally difficult. Of the 194 new cases reported by Warren and Ehrenreich, 32 involved the female genital tract, and in this series double cancers of the same or paired female reproductive

*Work done during tenure of R. S. McLaughlin Travelling Fellowship.

organs were excluded. Slaughter's 1,868 cases included 144 involving the female genital tract. Of these, 57 involved the ovary paired with the uterus, cervix, breast, or colon, all situations in which ovarian metastases are common and therefore the primary nature of the ovarian neoplasm is in doubt.

Watson,[13] in 1953, reported on 16,626 cancer patients in whom were found 1,171 multiple cancers. Of this group, including both surgical and autopsy cases, only 422 were of different organs and had pathological proof, and 126 of these included the skin or lip.

Stalker, Phillips, and Pemberton,[10] found 113 cases of multiple primary cancer among 2,500 cancer patients operated on in 1937. In 35 of these the skin only was involved and in 19 others the skin was one of the two organs involved. Forty-one cases involved the female genital tract, and of these 10 were bilateral ovarian tumors.

In spite of the voluminous literature on the subject of multiple primary cancers, very few reports have dealt exclusively or primarily with cases in which the female genital tract was involved. With few exceptions, papers dealing with this particular group consist of reports of small groups of cases or single cases. Marrangoni and McKenna[7] reported 15 such cases occurring in 618 multiple primary cancers, an incidence of 2.4 per cent of all the multiple primary cancers. This is 3 times the 0.8 per cent incidence reported by Warren and Gates. The criterion which Marrangoni and McKenna used was that "the distinction can be made when the tumors have entirely different histological characteristics." The validity of such a criterion would, of course, be completely dependent upon the thoroughness and extent of histologic examination of the tumors in question, as the wide variations of structure possible in even the most characteristic tumors is widely known. This is especially true in the case of endometrial and ovarian carcinomas.

Maliphant[6] commented on the rarity of simultaneous double primary cancers of the uterus, and quoted Frank as stating that as of 1931 no such case had been reported. Goldstine[3] reported a case of simultaneous squamous carcinoma of the cervix and adenocarcinoma of the fundus in 1935, Counseller and Butsch[1] reported two such cases in 1936, and Smith and Masson[9] reported a case in 1939. Our own series includes 3 cases of squamous carcinoma of the cervix and adenocarcinoma of the endometrium; in each case the occurrence was metachronous, with intervals ranging from 3 to 13 years.

The purpose of this paper is to present 54 cases of multiple primary malignant neoplasms found in patients of the gynecological cancer service of the Royal Victoria Montreal Maternity Hospital from Jan. 1, 1927, to June 30, 1955. In 9 of these patients, both primary cancers occurred in the genital tract, while in 19 of the remaining 45 patients the extragenital lesion was in the breast. Thus, in 28 of the cases both malignant neoplasms were derived from epithelium peculiar to the female sex and particularly subject to the effects of the various phenomena of reproduction.

Criteria for Acceptability of a Case as One of Multiple Primary Malignant Tumors

Billroth, as quoted by Warren and Gates, first described multiple primary malignant tumors in 1879, and at that time laid down 3 postulates to be used in establishing the primary origin of multiple tumors, viz., each tumor must have a distinctive histology, each tumor must arise in a different situation within the body, and each must give rise to its own metastases. Billroth's third requirement, that each tumor must give rise to its own metastases, has become increasingly unacceptable, as it is predicated on failure of treatment of either cancer. This is particularly so with respect to gynecological cancer, in which appreciable survival and apparent cure rates may be attained, thus increasing the potential opportunity for a second cancer to appear, while at the same time creating the possibility of there being no metastases from the first tumor.

Various other criteria have been adopted by subsequent writers, all of whom have rejected Billroth's postulates on these grounds. As already stated, Marrangoni and McKenna have accepted tumors as being of multiple primary nature when they have entirely different histologic characteristics. The validity of cases selected on such a basis alone appears to us to be too greatly dependent on the extent of histologic examination and the degree of pleomorphism of the tumors. In 1936 Counseller and Butsch reported 2 cases of simultaneous double cancer of the uterus, one case of which was an adenocarcinoma of the cervix, Broders' Grade III, and a confluent adenocarcinoma of the corpus, Broders' Grade II. Similarly, several of the 71 cases reported by Hurt and Broders[5] in 1933 are presented as double primary adenocarcinomas on the basis of different Broders gradings in otherwise quite similar histologic patterns. This also seems to us to be an insufficiently strict criterion to rule out the probability of one tumor being an extension, recurrence, or metastasis of the other.

The most generally used criteria are those of Goetze as quoted by Stalker, Phillips, and Pemberton, who stipulated that "The macroscopic and microscopic appearance of the tumors must be that of the usual carcinomas of the organs involved; exclusion of metastases must be certain; diagnosis may be confirmed by the character of the metastases in each case."

In the present series we have based our acceptance of multiple primary malignancies largely on Goetze's criteria. Tumors arising from distinctly different types of epithelium, and unmistakably characteristic of their parent epithelium in each case, for example, squamous carcinoma of the cervix and adenocarcinoma of the breast, large bowel, or endometrium, have been accepted as representing independent primary growths. In the event of both tumors being adenocarcinomas, we have required that each be completely typical of the usual type of tumor of that particular organ, both grossly and microscopically, and that other evidence of possible metastases from the first tumor be absent. All tumors were examined microscopically, and the diagnosis confirmed independently by a gynecological pathologist and a general pathologist, and in each case the double primary nature of the tumors in question was agreed to by both pathologists.

Analysis of Present Series

In a preliminary screening, 65 patients were considered to have had more than one primary cancer. The various tumor pairs were graded A, B, or C as regards the validity of their primary origin. Those in group A we considered unquestionably primary in origin, one tumor being of squamous-cell type and the other being adenocarcinoma in most cases. There were 46 cases in this category. The cases in group B were designated as of "probable" primary origin, and included the tumors of similar original cell type, although of characteristic gross and microscopic structure, location, and natural history. Cases in group B were acceptable to the writers as being of primary origin. There were 8

cases in group B. Group C consisted of the cases in which any reasonable doubt as to primary origin existed. This group of 11 patients was excluded from the series.

In the present series there were 109 primary malignant tumors in 54 women, and of these 109 tumors, 63 involved the genital tract. Eighteen of the 63 genital tract tumors occurred in 9 women. There were 5 patients in whom both tumors were detected simultaneously; in 3 of these patients both tumors involved the genital tract, and in the remaining 2 patients the extragenital lesion was in the breast.

There was one patient with three primary cancers occurring in the colon, breast, and cervix at 8 and 12 year intervals. One other patient with cancer of the breast developed cancer of the other breast after an interval of 10 years; and after a further 10 year interval developed a papillary cystadenocarcinoma of the ovary.

Only 3 cancers in our series involved the skin. Of these, one was a basal-cell tumor of the face, while the other two tumors were malignant melanomas.

There were 14 sites of origin of the various malignant neoplasms occurring in this series, as shown in Table I.

TABLE I. COMBINATIONS OF ORGANS INVOLVED IN MULTIPLE PRIMARY CANCER SERIES

	CERVIX	CORPUS	OVARY	VULVA
Corpus	3	–	–	–
Ovary	1	2	–	–
Vagina	1	1	–	–
Vulva	1	–	–	–
Breast	12	3	3	1
Stomach	–	2	–	–
Colon	4	2	3	1
Rectum	1	1	2	–
Bladder	1	2	–	–
Ureter	–	1	–	–
Pharynx	1	–	–	–
Brain	–	1	–	–
Skin	3	–	–	–
Thyroid	1	–	–	–
Leukemia	1	–	–	–

Ages at the time of detection of the first malignant tumor ranged from 28 years to 74 years, with an average of 52.6 years. It is an interesting sidelight that in the 2 patients at the extremes of the age range the two malignant lesions were detected simultaneously and that both patients are still alive, the younger after 18 years and the older after 3 years.

The interval between detection of the first and second tumors ranged from 0 to 21 years, with an over-all average of 7.6 years. In 36 instances the genital tract tumor occurred first or coincidentally, while in 27 instances it was the second tumor to occur.

The distribution of the genital tract cancers is shown in Table II, along with the total Royal Victoria Hospital distribution of these tumors, and the percentage of the latter which is involved in the multiple primary malignancy series.

TABLE II. DISTRIBUTION OF GENITAL TRACT CANCER

	MULTIPLE PRIMARY SERIES	ROYAL VICTORIA HOSPITAL TOTAL	% IN MULTIPLE SERIES
Cervix	29	1,055	2.75
Corpus	18	357	5.04
Ovary	11	321	3.42
Vagina	2	27	7.40
Vulva	3	53	5.66
Combined	63	1,813	3.47

From this table it may be seen that one woman in every thirty who developed a cancer of the genital tract either had, or was destined to develop, another cancer.

The cases involving cervix, corpus, and ovary were examined with regard to the relationships between the order of their occurrence and (1) age at detection, (2) interval between detection, (3) survival; comparison was also made with the total Royal Victoria Hospital experience for cancer of these organs. It was found that the average age of detection corresponded closely with the average age of detection of the entire clinic group, and the order of occurrence showed no demonstrable relationship to the interval between detection of the first and second tumors.

Survival of Patients With Multiple Primary Malignant Lesions

In comparing survival rates between cases in the multiple cancer series and the total Royal Victoria Hospital experience, one notes that all but one of the cancers of the cervix occurring in the series were in either Stage I or Stage II, in the ratio of 1.3:1.0. Comparison was therefore made with the total Royal Victoria Hospital Stages I and II, which were found to occur in the ratio of 1.0:0.94. These ratios apply to the groups of cases available for 5 year survival estimation. Corresponding ratios of 0.77:1.0 for the series and 0.82:1.0 for the Royal Victoria Hospital total were established for the Stage I and II cases available for 10 year survival estimation. In order to obviate the effect of this difference in stage distribution, corrected survival rates were calculated for the combined Stage I and Stage II of the total Royal Victoria Hospital experience. The corrected survival rates for Stage I and II carcinoma of the cervix, and the absolute survival rates for carcinoma of the corpus uteri and ovary are shown in Table III.

TABLE III. COMPARISON OF SURVIVAL RATES FOR CANCER OF CERVIX, CORPUS, AND OVARY, BASED ON ORDER OF OCCURRENCE IN MULTIPLE CANCER COMBINATION. FIGURES FOR CERVIX COMPRISE STAGES I AND II COMBINED

	MULTIPLE MALIGNANCY SERIES (ORDER OF OCCURRENCE)						ROYAL VICTORIA HOSPITAL TOTAL (%)
	FIRST		SECOND		TOTAL		
	NO.	%	NO.	%	NO.	%	
Cervix.—							
5 year	13	86.6	4	66.6	17	80.9	69.2
10 year	10	76.2	1	33.3	11	68.7	36.1
Corpus.—							
5 year	10	100.0	2	66.6	12	92.3	61.7
10 year	8	88.0	0	00.0	8	88.8	49.6
Ovary.—							
5 year	3	100.0	1	20.0	4	50.0	37.6
10 year	2	100.0	0	00.0	2	66.6	27.8

While the numbers involved are admittedly small, there was a considerably higher survival rate for gynecological cancer in the multiple cancer series as compared with the total Royal Victoria Hospital experience. This was especially marked when the gynecological cancer was the first of the multiple malignancies to occur; but even when the order of occurrence was disregarded, the 5 year survival rate was 11.7 per cent higher, and the 10 year survival rate 32.7 per cent higher for cancer of the cervix. In the case of corpus cancer the series 5 and 10 year survival rates were 30.6 per cent and 38.4 per cent higher than the over-all clinic results, while in ovarian cancer the series 5 and 10 year survival rates were 12.4 per cent and 38.8 per cent higher.

To view the increased survival of patients in the multiple cancer series from another aspect, a comparison was made between the percentage of the clinic total cases for cervix, corpus, and ovarian cancer which were found in the multiple cancer series, and the percentage of the total 5 and 10 year survivals which occurred in the series. In other words, the expected and the actual percentages of the total 5 and 10 year survivals for cancer of the cervix, corpus, and ovary were compared for those falling in the multiple cancer group. This is shown in Table IV.

TABLE IV. COMPARISON OF EXPECTED AND ACTUAL PERCENTAGE OF ALL 5 AND 10 YEAR SURVIVORS WHO HAD MULTIPLE PRIMARY CANCERS

	5 YEAR SURVIVAL		10 YEAR SURVIVAL	
	EXPECTED	ACTUAL	EXPECTED	ACTUAL
Cervix (Stages I and II)	2.7	7.4	2.7	9.4
Corpus	5.7	9.4	5.8	11.6
Ovary	3.8	5.3	1.9	5.1

From this table it may be seen that three times the expected number of 5 and 10 year survivals from cervix cancer occur in the multiple malignancy group, and that twice the expected number of 5 and 10 year survivals from cancer of the corpus and cancer of the ovary occur in the multiple malignancy group.

Etiological Significance of Multiple Primary Malignant Tumors

Does this indicate that individuals who have more than one cancer have more slowly growing tumors or greater resistance to the spread of their tumors, of does it simply mean that they have developed the second tumor because they have lived long enough to do so?

This question must remain unanswered until reliable estimates of cancer incidence are available. In 1932 Warren and Gates concluded that the occurrence of multiple cancer was more frequent than could be explained on the basis of chance, and postulated a predisposition or susceptibility to cancer in certain individuals as the explanation. In their continuing study of 1944, Warren and Ehrenreich calculated the incidence of multiple cancer as 11 times as great as could be explained on the basis of chance. However, nine years later Watson interpreted a comparable group of cases as indicating absolutely no increased incidence of a second cancer over and above the expected incidence. He based his calculations on Dorn's[2] figures for expected incidence, and these have been further substantiated by the recent work of Heller and associates[4] at the U.S. Public Health Service. It is clear that there is no agreement on this point, and that no such agreement can be possible until accurate data on cancer incidence become available.

One fact is clear, however. Multiple cancer is not a rarity. Therefore, it is urged that (1) all cancer patients be followed and examined yearly for the remainder of their lives, regardless of how certain one may be of the arrest of their cancer, and (2) any new symptoms or signs developing in a cancer

patient be thoroughly investigated with a view to possible treatment, and not automatically attributed to the original tumor and regarded as extension or metastases and therefore of hopeless significance.

Summary and Conclusions

1. Fifty-four cases of a second primary cancer on the gynecological cancer service are reported.

2. Sixty-three of the 109 primary cancers in this group involved the genital tract. This represents 3.47 per cent of all gynecological cancers seen in this clinic.

3. Appreciably higher 5 and 10 year survival rates for cancer of cervix, corpus, and ovary are found in the multiple cancer groups.

4. A plea is made for perpetual yearly follow-up examinations of all cancer patients, and for conscientious investigation of new symptoms in these women.

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PRIMARY NONPIGMENTED SARCOMA OF THE VULVA, WITH REPORT OF A CASE COMPLICATING PREGNANCY

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PRIMARY nonpigmented sarcoma of the vulva is an extremely rare type of tumor, as shown by the sparsity of cases in the literature, and the brief discussion allotted to it in textbooks. Certainly, it is an exceedingly rare complication of pregnancy. Any type of maligant growth of the vulva is unusual during the childbearing age, perhaps the most common such tumor being the melanoma.

Because of the location of the lesion in the case presented here, an anatomical definition of the term, vulva, will be mentioned. Taussig,[14] in his monograph on the diseases of the vulva, quotes Poirer and Charpy as follows: "The vulva can, therefore, be considered to include the following structures: the labia majora and minora, the mons veneris, the perineum, the clitoris and its folds, the Bartholin's glands, the vestibule of the vagina, the meatus of the urethra, and the hymen."

A review of the literature on primary nonpigmented sarcoma of the vulva shows no recent cases complicating pregnancy. One of the earliest collections of cases of vulvar sarcoma was by Blair Bell[3] in 1907, who found only 6 in patients under 30 years of age out of a total of 18 cases. In only one instance was the tumor in the region of the vestibule. Kehrer,[6] in 1929, referred to 77 cases of primary sarcoma of the vulva, which was apparently all he was able to collect from the literature. In 1937, Taussig[15] reported a case of liposarcoma of the labium majus occurring in a 29-year-old primipara. There was no relation to pregnancy. The tumor, although present as a small lump for about four years, had grown suddenly larger in a six-month period. Local excision was followed six weeks later by a unilateral vulvectomy and inguinal lymph node dissection. The patient died with widespread metastases about six months after the original enucleation of the tumor.

Taussig[15] suggested that, with modern staining methods, a few of the cases reported as other types of sarcoma in the older literature may have shown evidence of arising from the fatty tissue of the vulva. He quoted several characteristics of liposarcoma in general as described by Shaw in 1936. Included are the facts that they may grow slowly for several years, with a sudden increase in size; that the encapsulation does not suggest malignancy; and that they have a varied hisologic structure.

In 1928, a case of unpigmented sarcoma of the labium majus in a girl of sixteen years was reported.[8] It was of the alveolar round-cell type. There were widespread metastases less than four months after the tumor was originally noted. In 1937, congenital myxosarcoma of the left labium majus was described in an infant.[1] Death occurred within a few months. There were metastases to the lungs and the mediastinal lymph nodes. In 1939, a case of primary sarcoma of the vulva was reported by Bernstein[2] in a 45-year-old woman. It had grown slowly over a sixteen-year period to the size of a grapefruit. It was treated by local excision followed by radiation. A four-year follow-up showed no evidence of recurrence. In 1940, a case of fibrosarcoma of the vulva in a 7-month-old infant was described by Hauptman and Taussig.[5] Local excision was carried out, followed later by radiation to local recurrences and inguinal metastases, but the infant died with pelvic tumor masses about a year later.

In the recent literature only a few cases are reported. Service and Derbyshire[11] described in 1946 a pedunculated fibromyxosarcoma of the left labium minor in a 3-year-old girl. A local wide excision was performed. Five and one-half months later, metastases were found in the right inguinal lymph nodes. Keller,[7] in 1951, reported a large fibrosarcoma of the left labia in a 58-year-old patient. Sacrez and associates,[10] also in 1951, reported a case of rhabdomyoblastic sarcoma of the vulva in a 4-month-old infant. He believed this to be congenital in origin. Recently, in 1955, Buckingham and McClure[4] reported a reticulum-cell sarcoma of the vulva in a 33-year-old patient, which had grown to a considerable size in a period of a few weeks. She was treated by local excision of the tumor, followed by radiation therapy. The patient was asymptomatic up to six months later, although recurrent masses were felt in the pelvis at this time.

Even from this small group of cases, it is evident that the age incidence of this type of vulvar tumor is very wide, from birth to old age, and that the prognosis is poor at any age.

A 23-year-old married white primigravida, a nurse, was first seen on July 30, 1954, when she was admitted to the Obstetrical Service with a diagnosis of acute pyelonephritis in the seventh month of pregnancy. She improved rapidly on antibiotic therapy and was discharged, asymptomatic, on Aug. 10, 1954.

At the time of that admission, the patient offered no complaint of any growth of the vagina or the vulva, and none was noted on the physical examination. She was subsequently followed in the prenatal clinic, where a routine pelvic examination on Aug. 17, 1954, did not reveal any vaginal or vulvar growth. The patient later stated that she had noted a small mass, about the size of a pea, on the left side of the introitus a few days afterward. She first complained about it on Sept. 7, 1954, during a visit to the prenatal clinic. It was slightly larger at this time, and on examination it was considered to be merely a small cyst arising from the left side of the vestibule. Since the estimated date of confinement was Sept. 17, 1954, only ten days away, it was thought advisable to wait and remove it at a later date if necessary. The mass grew rapidly over the next few weeks, but apparently caused no symptoms. No further note was made of it. On Oct. 4, 1954, twenty-seven days after the patient had first complained of the nodule, and approximately six weeks after she had first noted it, she was admitted to the hospital in active labor.

Arising from near the lower portion of the inner margin of the left labium minor, was a nontender, pedunculated, moderately firm tumor (Fig. 1). It was oval in shape, and measured about 2.5 by 2.5 by 3.0 cm. It was hanging on an elastic, thin pedicle of mucosa which measured about 0.5 cm. in diameter and 2.5 cm. in length. The color resembled that of the labia minora except for a 1.5 cm. area of ecchymosis and ulceration on the anterior surface. The patient was seen shortly after admission by two members of the attending staff, who suggested removal of the mass at the time of delivery by ligation and transection of the pedicle at its base. The growth was considered to be benign, either a lipoma or a fibroma. After an uneventful labor of eleven hours, a normal spontaneous delivery of a 6 pound, 10 ounce, normal infant occurred over a right mediolateral episiotomy. At delivery, the tumor was removed by double ligation of the base of the pedicle



Fig. 1.—Sketch showing tumor hanging from pedicle on left side of the vulva.

with No. 00 chromic catgut sutures, followed by transection at the base. The specimen was sent to the pathology laboratory for routine examination, the report of which follows: "Accession No. 5314-54. The specimen received fixed in Bouin's solution consists of a firm spherical mass averaging 2.5 cm. in diameter. The cut surface has a pale fibrous homogeneous appearance. [Fig. 2.] On microscopic examination, the tumor is made up of two types of cells. The more frequent type is a spindle shaped cell with a small round ovoid nucleus and indistinct cell borders. These are arranged in interlacing cords and whorls. [Fig. 3.] The second type of cell is an irregular and bizarre giant cell with abundant sharply defined, somewhat basophilic cytoplasm. These latter cells are multinucleate, with nuclei which vary considerably in shape, size, and staining properties. They lie within the whorls of spindle cells, and vary from round, to polygonal, to rectangular in shape. [Figs. 4 and 5.] Elongated forms lie in the axis of the containing cords of spindle cells. An occasional bizarre mitotic figure is seen in these larger cells. In some areas the giant cells are quite sparse, but in other areas they are so numerous as to dominate the

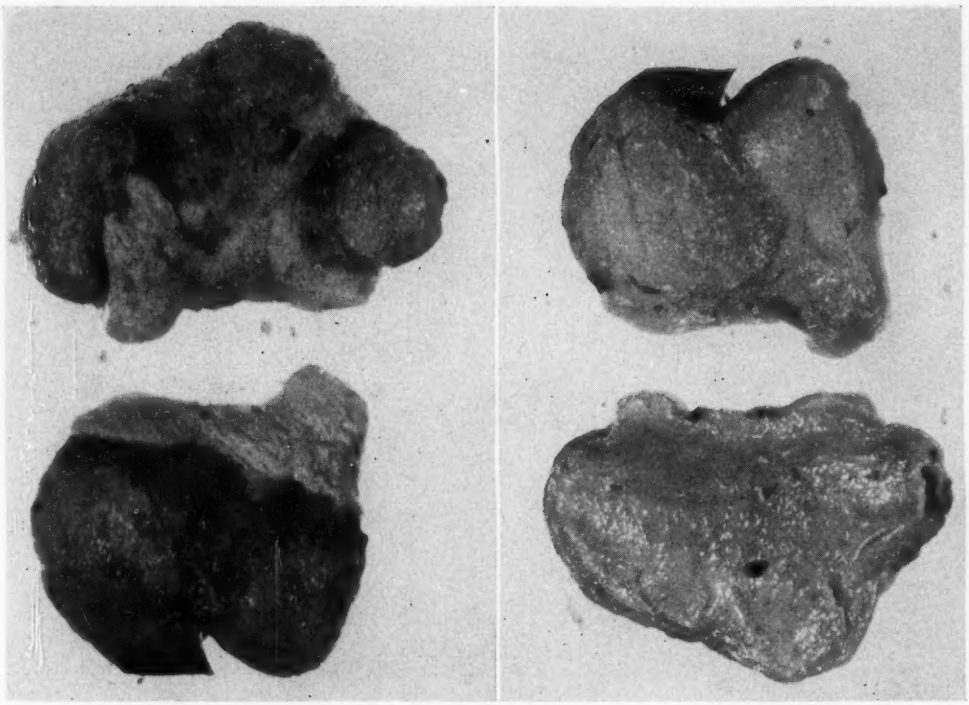


Fig. 2.—The photograph of the fixed specimen shows, on the left, the external surface of the two halves after the tumor had been split through the center. The lighter tissue represents chiefly the shrunken pedicle of mucosa. On the right are seen the cut surfaces of the two halves.

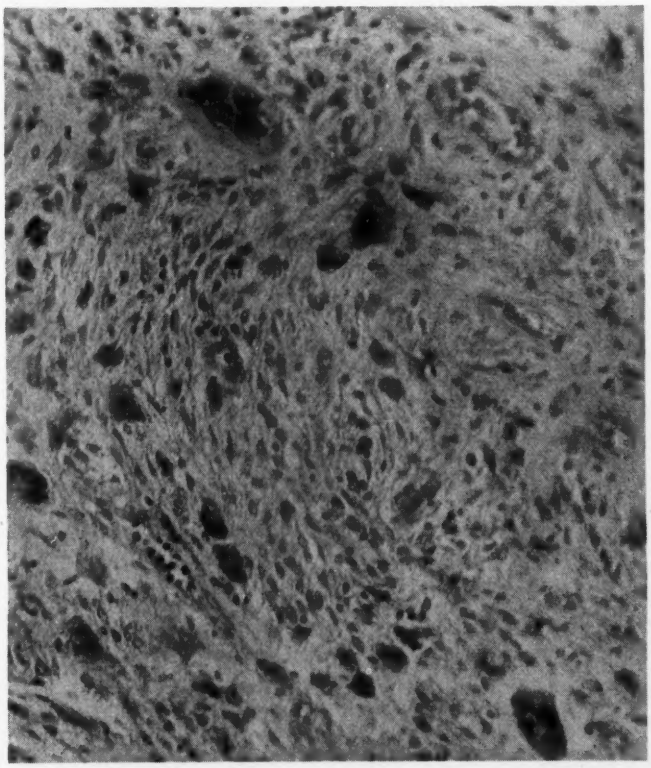


Fig. 3.—An area of somewhat loose fibrillar appearance. Many multinucleated large bizarre cells are present in a loose stroma. In the upper left-hand corner is seen a thin-walled blood vessel.

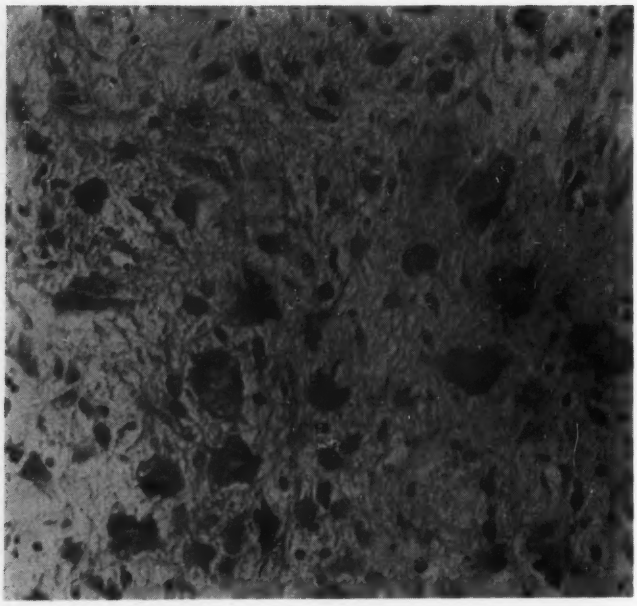


Fig. 4.—An area somewhat more fibrous in appearance. Many of the same bizarre multinucleated cells are seen interspersed among spindle cell whorls.

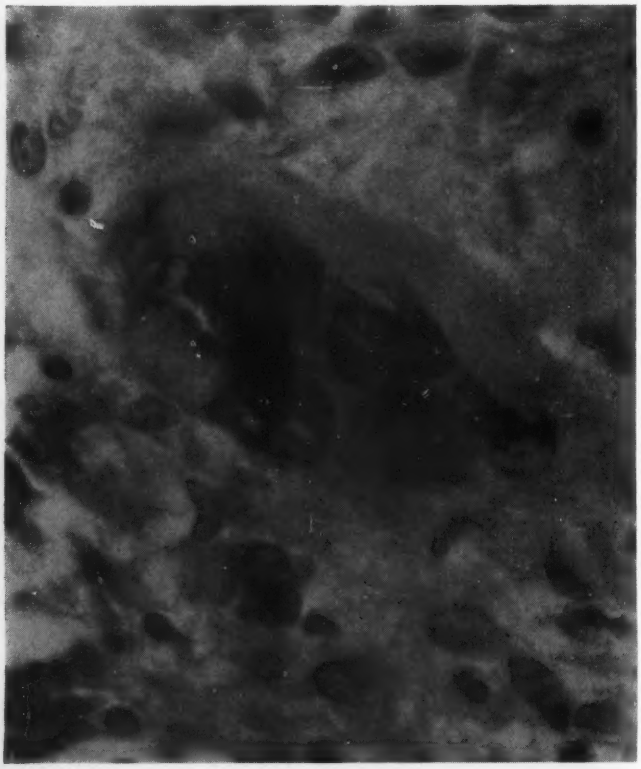


Fig. 5.—High-power view of a portion of the field.

microscopic field. The surface of much of the tumor is ulcerated, covered by fibrinopurulent exudate, and strikingly vascularized by capillary channels. At the edges, however, the tumor extends to the overlying squamous epithelium. This epithelium, though somewhat hyperplastic, is sharply demarcated from the underlying tumor by its intact basement membrane. With the trichrome stain, all of the fibrillar spindle cells or their intracellular substance stain green, and the cytoplasm of the giant cells is somewhat pinkish. No cross striations can be demonstrated in the bizarre giant cells.

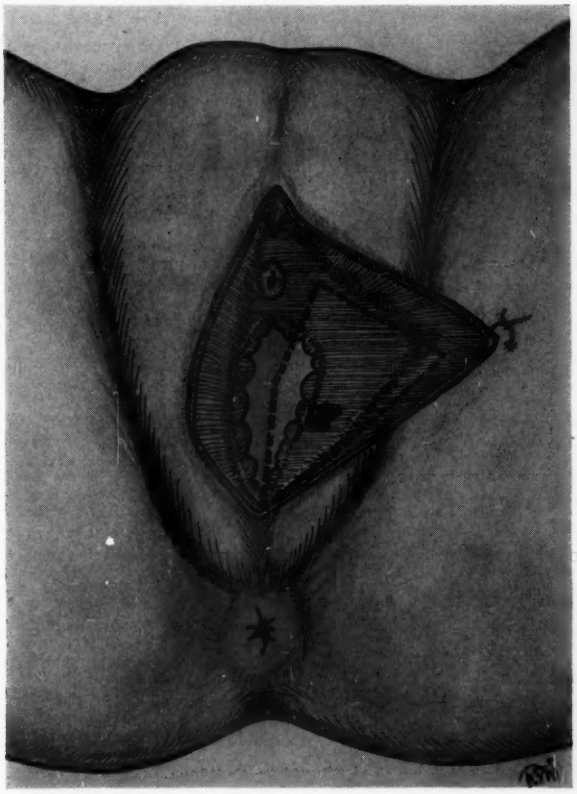


Fig. 6.—Sketch showing base of tumor pedicle as represented by the irregular, small, solid area on the left of the vestibule. The extent of excision is outlined by the dashes.

"Diagnosis: Sarcoma. Note: The exact character of this sarcoma cannot be determined. It may represent an atypical fibrosarcoma arising in the dermis with so-called spindle and giant cells. The elongated giant cells, often of 'strap' shape, suggest, too, the possibility of origin from striated muscle."

Following this report, the area of attachment of the pedicle was inspected. There was no evidence of induration on palpation. The inguinal lymph nodes were palpable bilaterally, but were small, shotty, and firm in consistency. It was recommended that a wide excision of the area around the base of the pedicle be performed. On Oct. 8, 1954, the patient was taken to the operating room, where a pelvic examination showed nothing abnormal other than the site of the recent excision. Just at the base of the hymenal ring, at about five o'clock, next to the inner surface of the left labium minor, there was a small irregular granular area, about 5 mm. in diameter. This small irregular area was identified as the base of the tumor pedicle. It was not indurated, and the underlying tissue was soft and freely movable. On the left side of the vestibule and the adjacent vaginal wall, and also including a small area on the inner surface of the left labium minor, a diamond-shaped area about 4 cm. by 4 cm. was outlined with the granular lesion at the center.

This was dissected out to a depth of about 1.5 cm. in the center (Fig. 6). Examination of this specimen showed no evidence of tumor. Follow-up examinations of the patient at frequent intervals have shown no recurrence. The inguinal lymph nodes have been negative. Repeated chest x-rays, and two skeletal surveys have shown no evidence of metastases during the period of sixteen months from the first observation of the tumor. It is of interest to note that her husband gives a history of the removal of a teratoma of the testicle over ten years previously, with no evidence of recurrence.

The tissue sections have been examined by Dr. Arthur Hertig and Dr. Emil Novak who considered it to be most likely a fibrosarcoma. Dr. Arthur Purdy Stout[13] considers the tumor to be a liposarcoma. His comment on the histology may be quoted: "The giant cells with bizarre pyknotic nuclei, the area of myxoid aspect, with a marked degree of vascularity, and the presence of occasional partly differentiated lipoblasts in the form of signet ring cells, are sufficient to establish the diagnosis." He feels that the tumor belongs to the variety of liposarcomas capable of metastasizing.

Comment

It is evident that if this tumor were present before the onset of the pregnancy, it must have been very small. Its rapid growth during the last trimester is probably coincidental, and unrelated to gestation. That sarcomatous change can occur in an ordinary lipoma or fibroma has been shown in well-documented cases.[9, 12] However, the likelihood that this neoplasm was probably malignant in type from its very beginning is indicated by the rapid growth from an unnoticeable size.

Summary

A case is presented of sarcoma of the vulva, originating in the vestibule at the base of the hymenal ring, in a 23-year-old white woman, during the last trimester of pregnancy. A fourteen-month follow-up has shown her to be symptom free. The pathology is described. The literature on primary nonpigmented sarcoma of the vulva is reviewed.

I wish to express my thanks to Dr. Albert M. Deal of Statesboro, Georgia, and to Dr. Henry C. Frech of Savannah, Georgia, for their most helpful cooperation in following this patient.

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THE VAGINOABDOMINAL APPROACH IN RADICAL PELVIC SURGERY

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WE OPERATE on those cases of carcinoma of the cervix in which, following treatment with radiation, there is evidence either of a poor response or, after what seemed a good response, signs of recurrence appear. In our first 27 cases we did the operation entirely within the abdomen in the extended Wertheim manner of Bonney, Meigs, and others. Two factors caused us to question this single approach. We developed what we considered altogether too high an incidence of bladder and rectal fistulas and, in two cases, we were informed by the pathologist that we have not removed sufficient vagina to clear the growth.

It seemed to us that one of the reasons why we were getting so many fistulas was the difficulty of finding an easy plane of cleavage from above through tissues greatly fibrosed by previous radiation therapy, with consequent damage to the base of the bladder and anterior surface of the rectum, already devitalized by radiation. Furthermore, we felt that in deciding where to cut the vagina off, we were doing so by guesswork rather than with a true appreciation of the downward extension of the growth. Having experienced in a small number of Schauta operations not only the certainty through sight and palpation of cutting the vaginal cuff well below the growth, but the great ease with which a proper plane of cleavage was attained as between the vagina and rectum and vagina and bladder, it was decided to adopt a combined approach. This has proved so satisfactory, not only in reducing the incidence of rectal and bladder fistulas, but in increasing the ease with which the latter part of the abdominal half of the operation can be done, that it is now our practice in all cases. Nor has the pathologist since been able to find evidence that we have not removed enough vaginal cuff.

The abdomen is first opened to determine whether the case is operable, as indicated by glands along the aorta or extensions to the lateral pelvic walls. If aortic glands are found, one or two are dissected out, and an immediate frozen section done on them. If they are positive the operation is abandoned. Where there is doubt as to the amount of extension to the lateral pelvic walls, a tentative dissection is done to see whether or not it can be cleared. If it is decided that the case is operable, the abdomen is closed with two or three through-and-through heavy silk sutures, a towel clipped over the incision, the operating sheet lifted up over the abdomen so that it still remains caught by its clips at the symphysis pubis, and the actual operation begun from below.

By starting from below in normal tissue unaffected by radiation we find ourselves immediately in a freely exploitable plane of cleavage, in which we are

able to work upward with great ease to, or almost to, the peritoneal reflection fore and aft. The incision is made about an inch below any area of induration, in tissue that not only looks but feels normal. As a rule this incision is about an inch above the urethral opening in front, and just above the levatores ani behind, but wherever it is it errs in taking away too much rather than too little vagina. (See Fig. 1.)

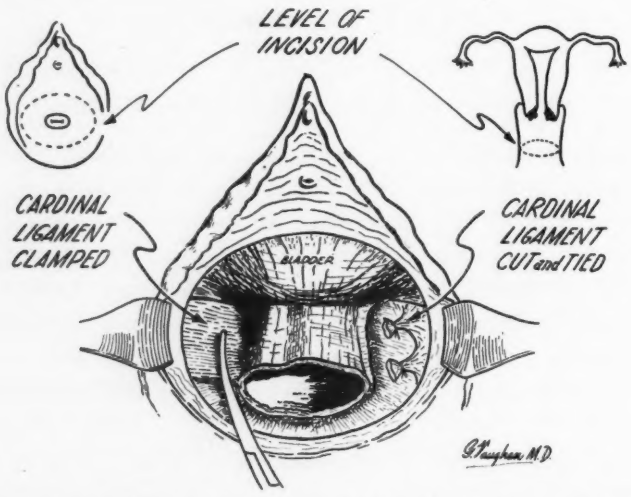


Fig. 1.—The vaginal approach—first step. While the level of the incision varies with the amount of extension down the vaginal walls, in most cases it is about as shown in the two smaller diagrams, or slightly above that level. The clamp on the cardinal ligament in the large diagram is placed further out than shown, and the pedicles retract further.

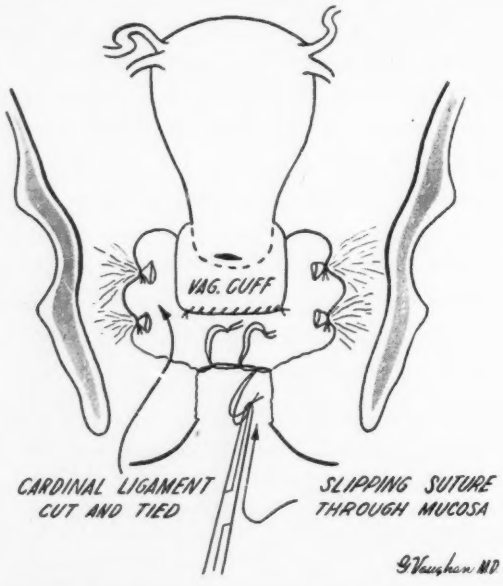


Fig. 2.—The vaginal approach—closure. The three sutures closing the vagina below are left about a foot long, knotted at the ends, and pushed up through the wound with a uterine dressing forceps. Note that the upper vagina and cervix are now held only by the upper third or half of the cardinal ligament.

Having achieved the proper plane of cleavage in front and back, the rectum and bladder are pushed away from the vagina with small gauze sponges on a regular sponge holder, with the scissors used to cut recalcitrant strands of

tissue. This dissection is carried as high as possible, with the use of deep retractors of the Heaney type to hold the tissues apart so that we can see clearly what we are doing. Usually the peritoneal reflection is reached posteriorly, but a point somewhat short of it anteriorly. On one or two occasions we actually broke through into the peritoneal cavity, but this is not done from choice, since the blood that seeps up from below later militates against easy dissection of the pelvic side walls. The further up this anterior and posterior dissection can be carried, however, the easier the last part of the abdominal half of the operation becomes.



Fig. 3.—The intravenous arrangement. Note that the blood and saline for each anterior tibial vein is on a separate stand, that the stands can be freely moved about the operating room, and that the tubing is long enough to permit this free movement without tension, and the likelihood of pulling the cannulae out of the veins.

The dissection is carried well out laterally, stripping rectum and bladder clear of the cardinal ligaments on each side far out toward the levatores ani and the pelvic walls. We now put forceps on these ligaments as far from the vaginal cuff as possible, and further out than shown in Figs. 1 and 2. Two bites on each side are taken as a rule, and both are tied off, as there is usually a fairly large artery in one or the other which, when it slips from the clamp, is not only difficult to pick up again but bleeds furiously. It is not so important to the future of the operation, however, to get both these two bites on the cardinals, as it is to separate the rectum and bladder thoroughly from the vagina as has been described. Sometimes, if the incision has been made higher up the vagina and if we are worried about the proximity of the ureter, only one bite is taken of the ligaments on each side.

The foregoing having been completed, the vaginal cuff is oversewn as tightly as possible so that it will retain any discharge from the cervix. Three sutures of No. 2 chromic catgut are then placed in the lower end of the vagina which are tied, left long, knotted at the long ends, and then shoved up through the incision into the pelvis with a uterine dressing forceps (Fig. 2). Later on, when the removal of the uterus has been completed, these long sutures makes it very easy to bring down the peritoneum back and front and complete the peritonization of the pelvis, thus not only covering completely the raw areas on

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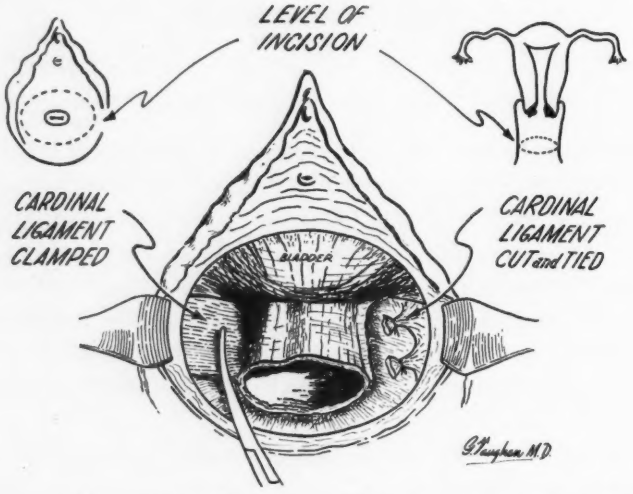


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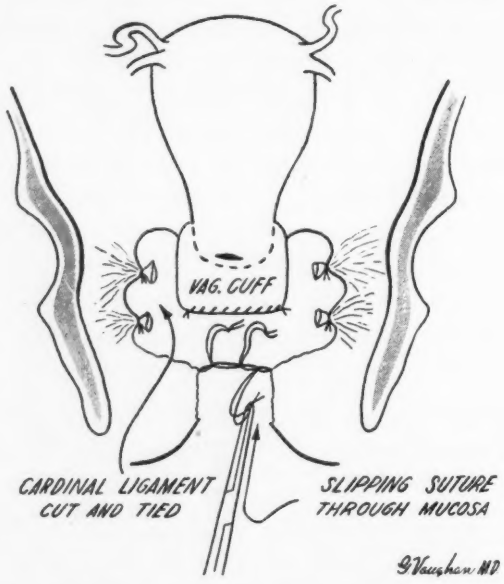


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the anterior wall of the rectum and the base of the bladder, but collapsing these areas on themselves. It is a troublesome thing to place these sutures in the vaginal stump from above and this prearrangement has proved a great help. Some operators do not bother about this peritonization. We feel that, along with the more easily dissectable plane of cleavage obtained by using the vaginal approach, it has helped in preventing fistula formation.

We now go back to the abdomen and, when the patient is flat, pull down the laparotomy operation sheet and, without removing it, simply place a clean sheet on top of it. This saves a considerable amount of time. Before going further a technical difficulty in thus moving from one field to the other and back again should be mentioned. In order to avoid disturbing the intravenous cannulae in the anterior tibial veins, in our earlier cases the vaginal part of the operation was done with an intern holding each leg. This proved such an awkward arrangement that we had extra long straps made to go around the ankles and now put the legs up in stirrups. To facilitate these moves from position to position the transfusion bottles hang from their individual stands on each side of the patient so that they can be moved easily headward or footward, and the rubber tubing is long enough to avoid awkwardness in moving the patient, and prevent any tension on the cannulae (Fig. 3). These may seem simple and trivial matters but lack of attention to them has made it necessary on occasion to cut down on the veins again to reinsert a cannula that pulled out. This is a long and tiring operation, and anything that shortens the time and increases the smoothness of performance is grateful to the operator's arterial tension.

Routinely, the gland dissection is carried about halfway up the common iliac, but if there are any palpable glands in the obturator fossa, or if the growth has extended very far out from the cervix we go the full length of the common iliac. The vessels are stripped bare, and we have found McKenzie clips very timesaving in dealing with the small branches that come off them, and which may cause troublesome bleeding if they tear back to the parent vessel.

We have not hesitated to remove the iliac vessels if these are involved by tightly adherent glands, as follows:

External iliac artery and vein	4 cases
External iliac artery and vein with internal iliac artery on the opposite side	1 case
External iliac vein	1 case

In none of these cases did gangrene supervene, although the affected foot was sometimes slightly colder for a few hours. Nor did we find that it interfered with early ambulation. In every case a postoperative sympathetic block was done. Gangrene has been reported in the literature following removal of the iliac vessels, and appears to be more prone to occur when the external iliac artery is removed. (Since this paper was written we have had gangrene occur in a case where the left external iliac artery and vein were removed. In view of the fact that we have one patient alive and well four years after removal of the external iliac artery and vein we would not hesitate to continue to do this when it is necessary—even if gangrene ensues—believing that it is better to be alive with one leg than dead with two.)

The gland mass having been pushed medially from the iliac vessels, the mass of gland-containing fat in the obturator fossa through which the obturator nerve courses is dissected medially.

The glands are now cleared from the internal iliac artery. This permits the vessels coursing forward from it to be easily identified, clamped, and cut close to the parent stem. The anatomy of these vessels varies widely from case to case and if the dissection toward them is made along the dotted line shown in Fig. 4

this variation may prove very baffling. Time is wasted deciding which vessel is which, and it is not impossible to mistake the obliterated hypogastric for the ureter. But if these vessels are early visualized as they come off the internal iliac and tied and cut close to it, the dissection that follows is not only easier but much more bloodless.

One of the bugbears of our earlier operations was a group of veins that runs toward the bladder deep in the pelvis along the upper edge of the cardinal ligaments close to the pelvic wall. These vessels tear very easily and sometimes the bleeding from them is quite furious. When we did tear them it always added half an hour to the operation, and in one case five extra bottles of blood had to be given before the bleeding was stopped. We now try, whenever possible, to avoid these veins. When they are torn, instead of wasting time and energy trying to pick them up, we lay strips of Oxycel over the area, with a sponge or two packed tightly against these, and the operation is continued elsewhere. Later, when the uterus has been removed and the area can be more clearly visualized, the bleeding point, which often by this time is no longer bleeding, can more easily be secured.

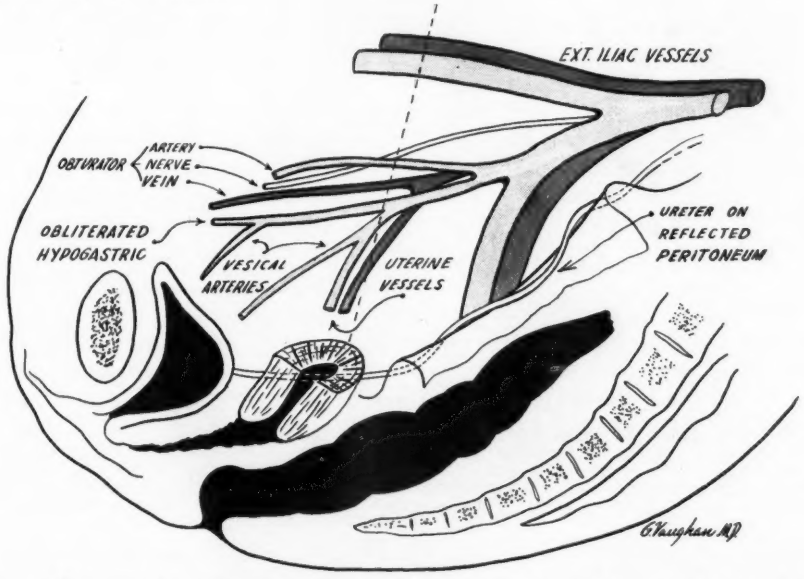


Fig. 4.—The vessels and ureter. The dotted line shows the usual place where the vessels coursing forward from the internal iliac are encountered. Their arrangement here is much more complex than where they first come off the parent stem. Note also the ureter, lying attached to its fold of peritoneum, where it is left while the dissection of both pelvic side walls is complete. The amount of ureter dissected free is approximately what runs in the diagram from the end of the peritoneal fold alongside the cervix to the bladder.

One of the difficulties in getting at bleeding points deep in the pelvis, especially in fatter women, is the length of ordinary instruments. Like others operating in this field we have found that an extra length in all instruments is a great advantage. We have also found that the Mann retractor keeps the field of vision clear in a most helpful way. McKenzie clips, which we have already mentioned, are very timesaving in clipping off small vessels.

Having cleared the pelvic side walls and pushed the mass of gland tissue medially toward the cervix, we do not dissect out the ureter on that side, but first go to the other side and repeat the gland dissection there. Only when that is completed is the clearance of the ureters undertaken. Left until this stage they are not only much easier to trace, but are less likely to suffer damage since, in the meantime, they are protected by their natural bed. A great deal has been written about preserving the blood supply of the ureter as a means of avoiding

fistula formation. Our own concession to this philosophy is (1) to clear as little of the ureter as possible, (2) to clear it as late in the operation as feasible, and (3) to refrain from handling it with forceps and tapes. Clearing it all the way from the pelvic brim to the bladder, carefully dissecting from it any ragged bits of tissue, and then putting a tape around it to drag it hither and yon is asking for fistula formation. We clear it back only far enough to be able to clamp effectively the uterosacral ligaments, and leave it as ragged as it comes. Although we catch it up with Babcock forceps while it is being dissected from the side of the cervix, once that is accomplished it is left alone, and pushed to one side when necessary with only a long sponge forceps; thus constant wear and tear on it are avoided.

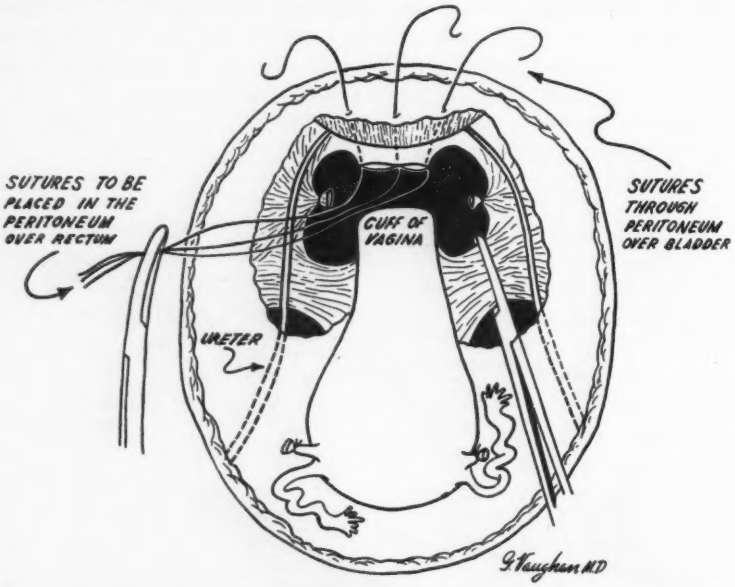


Fig. 5.—The situation when bladder and rectum have been dissected free. The uterus is held by the upper third or half of the cardinal ligament, which can be caught by one or two bites of the clamp. The clamp is placed farther out toward the pelvic wall than shown. The arrangement of the sutures which were thrust up from below through the vaginal vault is indicated as they are used anteriorly. They are not inserted until the uterus has been removed.

During the process of freeing the lower end of the ureter, the space dissected free in the vaginal part of the operation between the cervix and bladder is entered, and it is the ease with which this and the remainder of the operation can be done that is one of the great dividends of the double approach. In many cases the blood can be seen through the peritoneum, which alone has to be incised to reach the free space. Where there is difficulty because of fibrosis in getting through, the space is opened posteriorly, between rectum and vagina, and a finger pushed up from below between bladder and cervix to guide the dissection and so avoid injury to the bladder.

The full benefits of the vaginal approach now reveal themselves. The uterus and vaginal cuff, dissected free front and back, are held only by the uterosacral and the upper third of the cardinal ligaments. The increased ease with which these can be clamped close to the pelvic wall has to be experienced to be believed. Not only is a great deal of time saved but a considerable amount of difficult dissection deep in the pelvis avoided. Because one has access to the area of the growth not only from above but from below, one can work more freely and from two directions. This is particularly the case where the growth has extended rather far out on one side. One is able first to free the uterus on

the other side, and work toward this involved area from every possible angle, thus making sure of a wider removal of tissue, and avoiding serious damage to vessels.

While we prefer to clamp first what tissue we cut in this part of the pelvis, we do not make a fetish of it. In the occasional case it has been more expedient to cut first and clamp if there is a bleeder. Sometimes we have been able to get more tissue away by putting a clamp on these ligaments, putting tension on the clamp, and cutting out beyond the clamp close to the pelvic wall.

With the uterus out of the way the three long sutures which were tucked up through the vaginal stump from below are pulled up, the knots cut, and, after they are threaded on a needle, the wall of the rectum and the peritoneal reflection posteriorly, and then the bladder and the peritoneal reflection anteriorly are picked up. When these are tied to one another, not only is the pelvic floor completely peritonized, but the raw area on the anterior wall of the rectum and base of the bladder is collapsed on itself and considerably reinforced.

Removal of Bladder and Rectum.—We have tried to avoid removing both bladder and rectum and so getting a wet colostomy. For some reason, in the only cases in which we felt we might have to take both, the glands were clearly involved along the aorta or there was other extension that precluded the operation.

Where we realized on first opening the abdomen that the bladder would have to be removed, the vaginal part of the operation was modified by dissecting only a short distance upward between bladder and vagina, in fact, only high enough to get one bite with the clamp on the lower end of the cardinal ligament on each side. In most cases, the decision to remove the bladder was not made until fairly late in the abdominal half of the operation. We had to remove the bladder in 9 cases.

Fistulas.—One has only to read the papers of those who have reported their results to realize how serious the problem of fistula is to this type of surgery. With most operators it seems to be the ureter that is most commonly involved. Meigs[3] had 7 ureterovaginal fistulas in his first 100 cases; Benson[1] got ureteric damage of some sort in 20 of 127 cases, and Carter[2] had ureteric fistulas develop in 16 out of 188 cases. We have had only one ureteric fistula develop in our 60 cases and it, fortunately, healed spontaneously.

We have not been so fortunate with recto- and vesicovaginal fistulas. While Meigs and Benson seem to have suffered this complication only occasionally, Carter reported 15 vesico- and 3 rectovaginal fistulas in his 188 cases. We have had 8 patients develop such fistulas, 4 vesicovaginal, 2 rectovaginal, and 2 both vesico- and rectovaginal. In every case but one our fistulas of this type seemed to result from devitalization of the anterior wall of the rectum and base of the bladder due to dissection through and further interference with the blood supply of tissue already densely fibrotic from previous radiation given many months before. In all cases the dissection through this fibrosed area was difficult. The breakdown occurred from four days to several weeks following the operation.

All these fistulas but two occurred before we adopted the combined vaginal-abdominal approach. Of these 2 one was the result of extension of growth, as proved by a cystoscopy biopsy, and came on thirty-six days after the operation. We did an unwise thing in this case. A frozen section taken at the operation proved that there was invasion of the bladder wall close to the right ureter. We thought we might be able to preserve a competent bladder by removing the part of the organ involved. We should have removed the whole bladder.

We can report then that, in the first 27 cases where we used only the abdominal approach we got bladder or rectal fistulae in 6, but in the last 33

where we used the combined approach we have had only 2. We think that while the peritonization and reinforcement of the raw surfaces on the anterior wall of the rectum and the base of the bladder as previously described have also played a part in cutting down the incidence of these fistulas, these have not been as important as the other.

The bladder is usually drained for from two to three weeks postoperatively. There have been 4 atonic bladders, all of which have eventually regained effective tone.

We suspect that our freedom from ureteric fistulas is due to (1) leaving the ureter undissected until the last possible moment, so that for most of the operation it is protected from damage in its natural bed, (2) dissecting as short a portion of it free as is required but no more, and leaving it shaggy, and (3) leaving it free after dissection and pushing it aside as required only with a spongeholder rather than picking it up with forceps or tape.

There is one phenomenon arising from this operation that we have not seen stressed in the literature, but which has caused us considerable concern. It was pointed out to us by our charge nurse, who stated that she was having to deal with it in practically every case, that these patients become unusually depressed postoperatively on about the fifth or sixth day and that the depression persists for a considerable time. Just why it should develop to such a degree we do not know, but it is a factor that we now find ourselves having to combat with all the resources at our command.

The following are used: (1) a careful preoperative preparation of the patient's mind by a full explanation of what the operation may entail and the length of time that will be required for a proper recovery, (2) reassurance and bolstering of the morale by every means possible starting the day after the operation, (3) getting the patient up and around immediately so that she can sit and talk with other ambulatory patients, and (4) using drugs, of which we have found Largactil* the most valuable. While these measures have helped, they have by no means eliminated the phenomenon.

Summary

In summing up our somewhat meager experience with this operation we feel we can report that:

1. The combined vaginal-abdominal approach not only made the operation much easier to do but permitted a more thorough removal of involved tissue.

2. This combined approach, plus peritonizing the pelvic floor and so reinforcing the raw areas on anterior surface of rectum and base of bladder, very greatly cut down the incidence of vesico- and rectovaginal fistulas in the last half of our series.

3. Leaving the dissection of the ureters until late in the operation and dissecting free only the length required seems to have been responsible for our almost complete freedom from ureterovaginal fistulas.

4. We have had a high incidence of postoperative depression.

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2. Carter, B., et al.: Trans. Fifth Am. Congress Obst. & Gynec. (supp. vol. Am. J. Obst. & Gynec.) **64A**: 309, 1952.
3. Meigs, J. V.: Am. J. Obst. & Gynec. **62**: 854, 1951.

*Largactil—chlorpromazine, manufactured by Poulenc Ltd., Montreal, Quebec.

INTESTINAL OBSTRUCTION FOLLOWING PELVIC SURGERY FOR BENIGN DISEASE*

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INTESTINAL obstructions are problems which usually fall within the province of the general surgeon. However, obstructions do occur early following pelvic surgery. Therein, they become a problem for the gynecologist.

Nine papers on hysterectomy[1-9] and two on myomectomy[10-11] which have appeared in the literature since 1942 and which mention obstruction as a postoperative complication, report an incidence of early mechanical obstruction varying from 0.2 to 1.0 per cent and of adynamic or paralytic ileus varying from 0.7 to 8.2 per cent. In these papers a total of 7,890 operations were reported with 15 patients developing a mechanical obstruction and 74 an adynamic ileus. Using these figures, the over-all average incidence becomes 0.2 per cent for mechanical obstruction and 0.9 per cent for adynamic ileus. Thus, the incidence of early intestinal obstruction following pelvic surgery is low. Nevertheless, obstruction, particularly mechanical obstruction, is an exceedingly serious postoperative complication because of the high mortality rate which may occur.

These papers generally do not discuss the type of mechanical obstruction which occurs. It might be surmised, however, that the commonest type of mechanical obstruction encountered early, following pelvic surgery, will be of the adhesive type, since Becker,[12] in an analysis of 412 cases of acute adhesive obstruction occurring in the ten-year period, 1940-1949 on the Surgical Service of the Charity Hospital of Louisiana in New Orleans, found most (34.3 per cent) to follow (within four weeks) gynecological surgery. On the other hand, obstruction in several of the many other categories discussed by Wangensteen[13] will be expected to occur, but less frequently.

It is the purpose of this paper to determine the incidence and kind of intestinal obstruction occurring on a gynecological service without reference to any particular operation and to analyze and evaluate the procedures and regimens used for the diagnosis and treatment of this postoperative complication of surgery for benign gynecological pathological conditions. Obstruction following operation for malignant pelvic disease was not evaluated, for in many instances this complication is unavoidable.

During the five-year period between Jan. 1, 1950, and Dec. 31, 1954, 3,217 abdominal operations were performed on our service as shown in Table

*Presented at a meeting of the New York Obstetrical Society, Dec. 13, 1955.

I. Approximately one half of these operations were performed by attending gynecologists on private patients, the remainder by residents on pavilion patients. During the immediate postoperative period, within two weeks of the operation, 12 of these patients developed a mechanical obstruction and 18 a paralytic or adynamic ileus. Again, half of each of these were private patients. The over-all incidence of mechanical obstruction was 0.4 per cent and of paralytic ileus 0.6 per cent. But, as is shown in the table, considerable variability is seen to occur from year to year, being from 0.2 to 0.5 per cent for mechanical obstruction and 0.1 to 1.0 for paralytic ileus. Such variation can be expected in a sample of this size.

TABLE I. INCIDENCE OF INTESTINAL OBSTRUCTION

YEAR	NUMBER OF ABDOMINAL OPERATIONS	MECHANICAL OBSTRUCTION		ILEUS	
		NO.	%	NO.	%
1950	674	2	0.3	1	0.1
1951	683	3	0.4	4	0.6
1952	625	3	0.5	6	1.0
1953	620	3	0.5	3	0.5
1954	615	1	0.2	4	0.7
Total	3,217	12	0.4	18	0.6

Of the 12 patients with the diagnosis of mechanical obstruction 8 were reoperated upon. The diagnosis was confirmed in each case. Four were treated conservatively by intubation. One of the patients who was reoperated upon and one of those treated conservatively died. Of the 18 patients with the final diagnosis of paralytic ileus all were treated conservatively by intubation and all recovered.

The original diagnosis and condition encountered in those who developed either type of obstruction after the primary surgery are listed in Table II. Fibromyomas, as would be expected, were present in over half the cases. Pelvic inflammatory disease, however, was not a conspicuous entity. The case of early endometrial carcinoma was unsuspected at laparotomy and for this reason is included.

TABLE II. DIAGNOSIS OF CONDITION FOR WHICH LAPAROTOMY WAS PERFORMED

PATHOLOGY	MECHANICAL OBSTRUCTION	ADYNAMIC ILEUS
Myomas of the uterus	5	10
Myomas and pelvic inflammatory disease	2	1
Pelvic inflammatory disease	1	1
Ovarian cysts	3	2
Endometriosis	1	2
Stein-Leventhal syndrome		1
Endometrial cancer, early		1
Total	12	18

Obstruction occurred following hysterectomy in 18 patients, following myomectomy in 5, and as is indicated in Table III following other types of operations. During the period under study there were 1,876 hysterectomies and 327 myomectomies performed, making the incidence of obstruction following hysterectomy 0.8 per cent and following myomectomy 1.5 per cent. These figures do not, however, indicate any significant differences in the occurrence of obstruction following either of these operations as performed here, because at these low levels of occurrence with samples of these sizes, variation of this order of magnitude is to be expected.

TABLE III. TYPE OF OPERATION

OPERATION	MECHANICAL OBSTRUCTION	ADYNAMIC ILEUS
Total hysterectomy, salpingectomy and oophorectomy	6	9
Subtotal hysterectomy	1	2
Myomectomy	3	2
Bilateral salpingectomy or salpingectomy and oophorectomy	1	1
Oophorectomy	1	2
Wedge resection of ovary		1
Exploratory laparotomy for endometriosis		1
Total	12	18

The clinical signs and symptoms of mechanical obstruction become manifest on the average of about the fourth postoperative day and those of ileus on the average of about the third postoperative day. These average values, though, are not as informative as the data in Table IV which show the postoperative day the signs and symptoms became evident in each patient. It can be seen that there is a tendency for the mechanical obstructions to develop at almost any time postoperatively. Paralytic ileus, on the other hand, seems to develop more frequently around the third postoperative day with none later than the fifth postoperative day.

TABLE IV. DAYS ON WHICH POSTOPERATIVE SIGNS AND SYMPTOMS OF INTESTINAL OBSTRUCTION DEVELOPED

POSTOPERATIVE DAY	MECHANICAL OBSTRUCTION	ADYNAMIC ILEUS
1		
2	4	3
3	4	10
4	1	4
5		1
6	1	
7	1	
8		
9		
10	1	
Average	3.9	3.2

Of those with mechanical obstruction who were reoperated upon, the secondary surgery was performed within two days of the onset of symptoms in 5 of the cases; the 3 remaining patients were reoperated upon after five, six, and eight days of symptoms. The average lapse of time between the onset of symptoms and the secondary operation was 3.3 days. In 3 of the 4 with a final diagnosis of mechanical obstruction who were not reoperated upon, the obstruction lasted two days. The fourth patient died after five days of symptoms In those with paralytic ileus, the obstruction lasted from one-half day to nine days after the onset of the clinical signs and symptoms, with the average duration being 3.5 days.

The clinical findings are shown in Table V. As could be expected there is variation from patient to patient. Vomiting was more characteristic of mechanical obstruction, whereas distention was a more prominent feature in paralytic ileus. Pain was relatively insignificant in adynamic ileus whereas it was present in 83 per cent of the cases of mechanical obstruction. Fever was slightly more prominent in cases of paralytic ileus. Bowel sounds of all degrees were recorded in those with mechanical obstruction. As would be expected, bowel sounds were minimal or absent in those with paralytic ileus.

TABLE V. CLINICAL FINDINGS

SIGNS AND SYMPTOMS	MECHANICAL OBSTRUCTION	ADYNAMIC ILEUS
Distention	9	17
Vomiting	11	12
Pain	10	7
Tenderness	6	9
Fever	6	12
Bowel movements	7	5
Bowel sounds		
Hyperactive	4	1
Normal	4	
Hypoactive	4	6
Absent		10
Leukocytosis	5	8

An x-ray diagnosis of mechanical obstruction was made in all cases so classified. This was confirmed in the patients who were reoperated upon. An x-ray diagnosis of mechanical obstruction was made in readings of the first films in 5 cases which were ultimately diagnosed as ileus. It is possible that these 5 might have had some slight degree of mechanical obstruction which was masked and then relieved.

In the 8 cases of mechanical obstruction which required reoperation, the small bowel was involved in all and the primary fault was found to be adhesions to the operative site in 5 and a partial volvulus in 3. In one patient with adhesions the bowel was resected because it was thought the circulation was compromised, though the bowel was not yet gangrenous. The interval in this case between early symptoms of obstruction and secondary surgery was four days. Wound dehiscence was a complicating factor following the first operation in 2 cases. In one the mechanical obstruction was due to adhesions, in the other to herniation of the small bowel into the wound.

There was one death following reoperation. The original operation was a multiple myomectomy, 19 myomas being excised. This patient's postoperative course was complicated throughout by unsatisfactory oral intake and fever. Symptoms consistent with a partial bowel obstruction occurred two days before a wound dehiscence became evident on the fifth postoperative day. At exploratory laparotomy the small bowel which had herniated was reduced and the wound dehiscence closed. The patient died the following day, the sixth day following primary surgery, possibly from shock, peritonitis, and a questionable cerebrovascular accident. No postmortem was permitted. A critical review of her chart yields data which suggest that she was probably in fluid and electrolyte imbalance at the time she died.

Four patients were not reoperated upon. Of these, 3 responded after intubation for two days and replacement of electrolytes and fluid. The fourth died suddenly on the tenth postoperative day after five days of symptoms. A pulmonary embolism was suspected but no autopsy was permitted. A review of her chart also yields data which suggest that this patient was in fluid and electrolyte imbalance at the time she died.

With 2 deaths, the mortality rate in those with mechanical obstruction is 0.06 per cent if considered in terms of the 3,217 operations, but becomes 16.7 per cent of those with mechanical obstruction. There were no deaths among those who had paralytic ileus.

Of the 18 patients with adynamic ileus, 17 developed this as an unexpected complication of their postoperative course. In the eighteenth, the patient was maintained on intravenous fluids up to the time she developed the ileus. All the others were able to take some fluids and nourishment by mouth

following their operation and previous to the development of the ileus, but 13 received intravenous supplementation of fluid because of their poor oral intake.

Many of these patients became dehydrated, nevertheless. Twelve, or 67 per cent, had urinary output of less than 800 ml. in 24 hours at the time the first clinical signs of ileus became apparent. Only 6 had urinary output of 1,000 ml. or better, indicating adequate hydration.

An evaluation of the extent emesis contributed to the dehydration is impossible because unfortunately the volume of the emesis was measured and recorded accurately in only 6 of the cases. The dehydration indicated by the low urinary output in so many of these patients tends to emphasize the fact that these patients did not have their fluid losses adequately replaced, even though an evaluation of the saline infused during this period indicated that an attempt was made to replace salt and water lost in the vomitus. However, accurate replacement of fluid is impossible without accurate knowledge of the amount of fluid lost.

Treatment of adynamic ileus was essentially classic, tubes, enemas, and stimulants being used as indicated in Table VI. Once the ileus was established, fluid and electrolyte therapy was reasonably satisfactory in most cases in so far as water and sodium chloride are concerned. Immediately antecedent to the period covered in this study several investigators[14-17] had shown fairly clearly that ileus can occur during a potassium deficiency. It was also suggested[18] that, in many patients with ileus, potassium deficiency might be the etiological factor. It becomes of interest, therefore, to evaluate the use of potassium in the treatment of ileus in these patients.

TABLE VI. TREATMENT OF ADYNAMIC ILEUS

Tubes.—	
Levin	8
Miller-Abbott	2
Both	5
Rectal	8
Enemas.—	
Magnesium sulfate, glycerin and water	13
Milk and molasses	2
Soapsuds	2
Stimulants.—	
Prostigmine	8
Pituitrin	1
Heat or stupes	4
Castor oil	1

Only 2 of these patients received supplemental potassium before the development of the ileus, even though their intake of fluid and nourishment was inadequate in most cases. The amount of potassium received by these patients during the ileus is shown in Table VII. This shows the duration of the ileus as a function of the amount of potassium received. Five patients received no supplemental potassium during the ileus. Thirteen did, in the amounts shown. An adequate dose of potassium, under such circumstances, as determined from data published in the literature and from unpublished data of one of us (R. W. B.) obtained in studies of more complicated cases than those reported here, is of the order of 60 or more milliequivalents of potassium per day. With this value as a minimum figure, most of these patients received suboptimal doses of potassium. The one patient who received

80 meq. of potassium per day had a well-documented ileus which lasted only one half a day, and was one of the 2 patients who had been received potassium before the development of the ileus.

TABLE VII. POTASSIUM ADMINISTERED DURING ILEUS

DURATION OF ILEUS (DAYS)	MEQ. POTASSIUM RECEIVED PER DAY								
	NONE	0-10	10-20	20-30	30-40	40-50	50-60	60-70	70-80
	(NO. OF PATIENTS)								
1	3								1
2	1			1	1		2		
3			1						
4				1	1				
5						2			
6	1					1			
7					1				
8			1						

Serum potassium levels were obtained once or more times in 17 of these 18 patients. The values used are either those obtained at the first appearance of the symptoms of ileus or the first obtained thereafter. As is shown in Table VIII, 10 had serum potassium levels below 4.0 meq. per liter, a value which we consider from unpublished data of one of us (R. W. B.) to be the lower limit of normal for gynecological patients. Six of these 10 were dehydrated at the time this value was obtained, indicating that the actual hydrated serum value would be still lower. Seven exhibited values within the normal range. But 5 of these 7 were dehydrated, so they might possibly have shown subnormal values if they had been adequately hydrated.

TABLE VIII. SERUM POTASSIUM LEVELS IN EARLY ILEUS

PATIENT	SERUM POTASSIUM	
	NORMAL*	SUBNORMAL
Hydrated	2	4
Dehydrated	5	6
Total	7	10

*Normal range 4.0 to 5.5 meq. per liter.

A protein deficiency has also been implicated as a possible etiological factor in the development of ileus.[19] Therefore an attempt has been made to evaluate the protein stores of these patients at the time of the development of or during their ileus, as was done with potassium. If serum albumin values were obtained, these values are used preferentially as an indicator of the state of the protein stores. If no serum albumin values were obtained, either hemoglobin or hematocrit values were used. A serum albumin value of 4.0 Gm. per cent, a hemoglobin of 10.0 Gm. per cent, and a hematocrit of 33 per cent are used as the lower limits of normal. Values below these figures are taken to indicate a protein deficiency.

Using these criteria, and evaluating them again in view of the state of hydration of the patient, as was done with the serum potassium values, one notes in Table IX that 10 of them appear to have deficient protein stores. The remaining 8 had blood values within normal limits, but 6 were dehydrated. Thus some of these might well have had values indicative of deficient stores if they had been adequately hydrated.

Cognizance was taken of the protein deficiency in a few of these patients since 3 received a total of 500 ml., 3 received 1,000 ml. of whole blood, and 2 received 500 ml. of whole blood and 300 ml. of plasma during their illness. The remaining 10 received no blood or any other protein while they were maintained on parenteral fluids.

A brief retrospective criticism of the treatment received by these patients with adynamic ileus might be in order. It can be pointed out that most of them became dehydrated before the development of the ileus secondary to inadequate oral intake and vomiting. Intravenous fluid intake during this period was not adequate possibly because fluid losses were not measured in many instances. Once the ileus had developed, the treatment seemed adequate from the point of view of relieving distention, dehydration, and sodium chloride losses, but was definitely inadequate from the view of treating existing potassium and protein deficiencies.

TABLE IX. PROTEIN STORES IN ILEUS

PATIENT	PROTEIN STORES	
	NORMAL	SUBNORMAL
Hydrated	2	4
Dehydrated	6	6
Total	8	10

Comment

The incidence of mechanical obstruction and paralytic ileus in this series is similar to that reported in the literature to follow hysterectomy or myomectomy. From statistical considerations, using the data presented in the literature, one might expect most large series of pelvic operations to have a postoperative incidence of mechanical obstruction somewhere between 0 to 1 per cent and of adynamic ileus somewhere between 0 to 1.5 per cent. Even then there would be some series which would vary beyond these upper limits. In smaller series or samples much greater variation would be expected. These results would be expected only if the samples were drawn from the same population. Obviously they are not since not only patients and surgeons but also preoperative, operative, and postoperative procedures vary. So do methods of classifying and recording data, so that, for instance, unexpected adynamic ileus might not, in some instances, be recorded as such.

Since the etiological pathways through which either mechanical obstruction or adynamic ileus might develop are many, it would not be expected that any definitive data on etiology will be evident in this small series. Preoperative workup did not show these patients to be distinctively different in any particular way from many others who did not develop an obstruction. As already stated the pathological conditions and operative procedures were usual. Such factors as anesthesia and operating time did not seem to be of any etiological significance. Nor did the type of anesthesia used. Perhaps of some significance was the fact that 4 of those who developed mechanical obstruction and 8 who developed an adynamic ileus had had previous laparotomies. Five of these had lyses of adhesions at this operation. It is impossible

to know, without control data, if these factors are of any significance. The role which peritonitis plays in the development of adynamic ileus becomes difficult to evaluate with the present use of antibiotics.

As would be expected, the clinical findings varied somewhat in each case, but in both mechanical obstruction and ileus were essentially classic. Pain and bowel sounds were prominent in mechanical obstruction; distention, absence of bowel sounds, and fever in ileus. The radiological findings were helpful but not always definitive in differentiating mechanical obstruction from ileus.

That mechanical obstruction is a serious postoperative complication is emphasized by the 2 deaths in this small series. Since an autopsy was not permitted in either case the cause of death remains unknown. A review of the charts shows that neither of these patients received what we now would consider the best supportive treatment with fluids, electrolytes, and protein. It is not necessarily meant to imply that better treatment with these agents could or would have prevented their demise; however, as a patient begins to develop signs of obstruction her parenteral regimen should be one which will maintain her in the best possible physical condition. Then, if the final diagnosis is mechanical obstruction, the patient is a better candidate for reoperation; if ileus, she might recover more promptly.

The patient can be maintained in the best metabolic condition if kept hydrated, given adequate potassium and if necessary protein. This type of regimen applies equally well to patients who are developing either a mechanical obstruction or an adynamic ileus, and will be discussed presently with the stress on adynamic ileus, but applies equally well to patients developing a mechanical obstruction up to reoperation and obviously immediately following the second operation after which there will be an expected ileus.

If adynamic ileus can result from a deficiency of potassium or protein or of both, one might ask how patients recover without receiving either potassium or protein. Objective data are not available to give the answer to this question. Most probably spontaneous recovery will occur when the body spaces have contracted to the point at which the concentrations of potassium and protein in the body fluids are again adequate. If salt and protein losses, however, exceed water losses, spontaneous recovery would be impossible. If this is so, certain aspects of modern treatment of ileus could be considered incorrect unless potassium and protein are administered. Space does not allow an exhaustive discussion of this point, however.

More practically, if adynamic ileus can result from a deficiency of potassium or protein or both, one might ask if postoperative ileus due to such deficiency can be prevented, and if so, how. We have already analyzed the course of these 18 patients during the interval between their operation and the onset of the ileus and have noted that 14 of them did not make progress during the immediate postoperative period with respect to oral intake of fluid and nourishment and had to be given fluids intravenously. We have also noted that only 2 of these 18 received supplemental potassium before the

development of the ileus and that only one of them received potassium in anywhere near adequate amount. Therefore, if a patient does not make normal progress postoperatively with respect to oral intake and needs to receive fluid intravenously to supplement her intake, potassium should be administered in the supplemental fluid if there is an adequate urinary output.

An adequate urinary output can be maintained in such patients by administering not only enough salt and water for urine output and enough water for insensible loss, but also enough to replace that lost by vomiting. Correct replacement of any body fluid lost can only be accomplished if the volume lost is known. Therefore, vomitus must be accurately measured and recorded. Obviously, the volume of any fluid collected by suction must also be measured and recorded. An accurate check on the collecting and recording of fluids lost can be maintained by weighing the patient daily.

If under these conditions potassium is to be given it should be administered in amounts not less than 60 to 80 meq. per 24 hours and should be continued at that rate as long as there is an adequate urinary output and until the patient's oral intake is sufficient. No danger is involved if potassium, as potassium chloride, is administered to a well-hydrated patient in amounts not exceeding 40 meq. per liter of any other aqueous solution such as physiological saline or glucose and water. In the interval between the operation and the development of the clinical signs of ileus, most of the patients who received intravenous fluid to supplement their oral intake received more than the amount necessary to administer the 80 meq. of potassium suggested. When the patient tolerates fluids by mouth it is often advisable to administer potassium chloride in unsalted broth, using 20 meq. of potassium chloride per serving of broth. When potassium is administered parenterally the serum potassium levels should be determined to be sure they do not become unduly elevated.

In the patient with ileus, if there is not a prompt improvement in the first 24 to 48 hours following the potassium administration, the protein stores should be evaluated, and if deficient, replenished. With this regimen unexpected postoperative adynamic ileus due to potassium or protein deficiency may possibly be obviated and will certainly be ameliorated.

Summary

1. Intestinal obstructions occurred in 30 patients within two weeks after 3,217 abdominal operations for benign gynecological disease, performed at the New York Hospital during the years 1950-1954. Twelve of the cases were diagnosed as mechanical obstruction, 18 as adynamic ileus, giving an incidence of 0.4 and 0.6 per cent, respectively.

2. Hysterectomy and myomectomy were the most common operations, but both mechanical obstructions and ileus occurred after other types of pelvic surgery.

3. The commonest indication for the operation was fibromyomas.

4. The clinical findings in mechanical obstruction and ileus were essentially classic, pain and bowel sounds being prominent in mechanical obstruction; distention, absence of bowel sounds, and fever prominent in ileus.

5. The treatment for mechanical obstruction was operative in 8, intubation only in 4, with parenteral maintenance in all cases. The diagnosis of mechanical obstruction was confirmed in those reoperated upon. There was one death in this group. Of the 4 treated conservatively, 3 recovered and one died.

6. The treatment of adynamic ileus consisted chiefly of intubation with parenteral fluid maintenance until bowel sounds returned.

7. Once symptoms of ileus had been established, analysis of the fluids and electrolytes used for maintenance was satisfactory with respect to water and sodium chloride but probably not with respect to the use of potassium and proteins.

8. Analysis of management of patients who developed ileus shows that the critical period might be the time before the development of all the clinical signs and symptoms. During this period most of these patients became dehydrated, and received no supplemental potassium. Based on these findings it is suggested that closer attention should be given to patients during the immediate postoperative period who fail to progress normally with respect to oral intake.

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Discussion

DR. HENRY S. ACKEN, JR.—This complication of gynecological surgery is an infrequent one but a most distressing one. I was very much interested in Dr. Boynton's paper and his point of view with regard to potassium. It may well be a very important one. I think, however, there are two other factors that should be seriously considered in this situation. Mechanical obstruction can occur as the result of some fault in the technique of operation, particularly lack of proper peritonization of denuded areas. The question of infection is also of the utmost importance. Those of us who operated in the

days before antibiotics encountered the problem of adynamic ileus much more frequently than we do today and the general feeling then was that infection played a major part in it. Dr. Boynton has stressed one facet of this problem but has left untouched two extremely important factors.

DR. NELSON B. SACKETT.—I would like to ask Dr. Boynton, if he looked into the matter of duration of operation and into the type of anesthesia given. I had an idea that anesthesia, particularly, had something to do with this.

DR. BOYNTON.—We did look and had some cognizance of operative technique and infection and so forth. The interesting thing was how long most of these operations took and also the anesthesia. Invariably they ran around three hours and the anesthesia was primarily done by nurses. As you know, at New York Hospital they do not allow combined anesthesia, in other words, curare-ether, to be administered by the nurses. Only the attending doctors use it. Whether or not that played a part I do not know.

DR. SACKETT.—Ether?

DR. BOYNTON.—Cyclopropane and Pentothal. I guess in all long procedures the anesthesia would run 15-20 minutes longer sometimes than the operations due to the fact that the medical students were examining the patients after they were put to sleep and before they were wheeled into the operating room, which is an important factor.

DR. HUGH R. K. BARBER.—Approximately 50 per cent of these were cases of myoma, and I judge that they were apparently bleeding for some time before they came to operation. It has been my impression that such patients can have a normal hemoglobin and hematocrit, but still have a contracted blood volume and be in a state of chronic shock. Postoperatively, they have a course very similar to that which was pointed out here and does not necessarily represent a potassium imbalance. It would be good to have some comment on this particular aspect of the problem.

As I judge it from the slides, there was no attempt made to find out whether these patients had a contracted blood volume or not. Also, the story of dehydration was repeatedly brought up as a complication of the early postoperative period. It has been my impression that if there is dehydration, there also will be an increase in the extracellular potassium at that early phase. This is at variance with findings in the paper.

The other thing is that there was a comment which ran through the discussion about the decrease in plasma proteins. There did not appear to be any attempt to correlate this with anything else such as a calcium determination or an albumin-globulin ratio.

The last point is this. These patients had vomited, and it is my impression that there first occurs a hypochloremic alkalosis, which is accompanied by a contracted extracellular space and by dehydration. At this point the potassium is probably elevated in the extracellular space. If you have a hypokalemic alkalosis the extracellular space may be expanded which is different from the values for a hypochloremic alkalosis. This also is at variance with the findings in this paper.

DR. BOYNTON.—I do not know anything about that. These patients were supposedly normal patients, not anticachectic, beaten down, worn out. They were prepared for routine normal gynecological surgery and were thought to be in good shape. When the ileus developed, or obstruction, then the chemistry determinations were taken. I don't recall any calcium determinations being made. If so, we did not study them.

I might say somebody says an expert is a person far away. My expert on this is Dr. Bonsnes, a biochemist, and he is in Chicago. He could probably answer these questions better than I can so I will have to leave it at that.

DR. JOSEPH N. NATHANSON.—Did Dr. Boynton have any particular evidence as to the age factor? In other words, did obstruction or ileus occur in the old as opposed to young patients? What effect has early ambulation had with regard to the occurrence or frequency of intestinal obstruction?

DR. BOYNTON.—So far as we know they are all up early. As far as age distribution is concerned, there was nobody particularly old, actually. As a matter of fact, looking them over I thought they were a little on the young side, in the late thirties, early forties.

DR. LOCKE L. MACKENZIE.—Victor Bonney was always concerned about the possibility of mechanical obstruction of the intestine following myomectomy, depending upon the location from which the myoma was removed. Indeed, he felt so strongly about this that he would not remove a myoma from the posterior surface of the uterus in the neighborhood of the uterosacral ligament. Has Dr. Boynton found that removal of myomas from this area tends to increase the amount of mechanical obstruction following?

DR. ARTHUR DAVIDS.—In answer to Dr. Mackenzie, I reported our series of 1,150 myomectomies approximately four years ago and since then have added another 400 cases. There were no deaths from intestinal obstruction in this series. We try to limit the number of incisions in the uterine wall and attempt to remove as many fibroids as possible through the primary incision. We make no restrictions, however, as to site or number of incisions which may be necessary to perform a thorough myomectomy. The prevention of intestinal adhesions with subsequent obstruction is accomplished by complete peritonization of all the uterine incisions. We utilize the bladder flap of peritoneum to cover the incisions in the anterior wall and in many instances attach it to the superior aspect of the fundus if necessary. Incisions in the posterior wall of the uterus are peritonized by one of the following methods: sewing the omentum or the sigmoid itself over the lines of incision, attaching free omental grafts to the uterine wall, or suturing the ovary and uteroovarian ligament over the incision. We perform extensive myomectomies involving the removal of as many as 80 to 90 fibroids and intestinal obstruction has never been a problem. This I am sure is due to the careful peritonization of all uterine incisions. A private patient was admitted recently with intestinal obstruction 21 days after myomectomy which was relieved by surgical intervention. This was the only instance of obstruction in our series.

DR. BOYNTON.—Have you had any following cesarean section?

DR. DAVIDS.—I do not think that we have had any cases of intestinal obstruction following cesarean section since the beginning of our service three years ago. We have performed about 700 sections.

I should like to point out that in some of your cases of ileus the operating time was unduly long. This might have had a decided effect on the incidence of such complications. I believe that the incidence of adynamic ileus in the absence of infection will be proportionate to the degree of intestinal manipulation and the length of time that the mechanical procedure lasts. I do not believe that the length of operation per se will influence the incidence of mechanical obstruction.

THE STEIN-LEVENTHAL SYNDROME: ANALYSIS OF 43 CASES WITH SPECIAL REFERENCE TO ASSOCIATION WITH ENDOMETRIAL CARCINOMA*

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IN 1935, Stein and Leventhal[29] first described a syndrome consisting of menstrual irregularity featuring amenorrhea, a history of sterility, a masculine type of hirsutism, obesity, and, less consistently, retarded development of the breasts. The ovaries were similarly and simultaneously enlarged as the result of typical cystic changes that were irreversible and refractory to therapy with hormones. The condition did not appear to be congenital in origin or on an inflammatory or degenerative basis. It did possess many of the features of a genuine endocrine disturbance. Since this original contribution, numerous papers have appeared reporting on single instances or on small series of patients with the condition.[2, 7, 11, 13, 22, 24–28, 30] A number of possible theories regarding etiological factors have been explored and discussed.

It is the purpose of this paper to review the clinical and pathologic features of a group of patients with this syndrome who were seen at the Mayo Clinic. Special emphasis will be placed on the frequent association of endometrial carcinoma occurring as a late manifestation of the syndrome, an aspect that heretofore has been somewhat neglected.

General Background

Stein and Leventhal[29] envisioned that the polycystic ovarian alterations were basic and that they were related to abnormal pituitary-hormonal stimulation, with the formation of capsular ovarian fibrosis that acted as a bar to normal ovulation. According to Bailey,[1] a deficiency of pituitary stimulation resulted in secondary cessation of ovarian function. Arrest of follicular maturation led to the observed polycystic ovarian condition and perhaps also to chronic cirrhosis of the peripheral tunic and the central stromal core.

Ingersoll and McDermott,[13] in their study of 21 patients with the syndrome, were impressed by the absence of formation of corpora lutea. Obtaining normal values for follicle-stimulating hormone in 3 of their patients so studied, they theorized that the deficiency was in the luteinizing factor of the pituitary. The net result was the formation of large numbers of maturing follicles that lacked the "push through" to ovulation. Many of these follicles underwent atresia, while others were in the process of development. Their theory that the cause of peripheral ovarian fibrosis is congenital faces the drawback that some of the patients had menstruated and even had borne children prior to the onset of the symptom complex.

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DuToit[7] considered that the thickened ovarian rind observed in these patients was secondary to formation of cysts and that it was related to absence or defective development of the thecal cone. Reynolds,[21] Delson,[3] and Vara and Kalevi[36] concentrated their attentions on circulatory ovarian disturbances as a cause of the polycystic change. The development of hemorrhagic cysts in the ovaries of animals was observed to straighten out segments of the spiral artery. Abnormal increases in arterial pressure in these straightened segments theoretically could interfere with nutrition of the ovaries, especially during the growth phases of follicular maturation, and lead to formation of cysts. An observed high incidence of follicular cysts in uterine retroversion with passive congestion of the ovarian hilus has been adduced as contributory evidence favoring this "vascular" hypothesis.

Symptoms and Signs.—In Stein and Cohen's[27] series of 28 patients, 25 complained of amenorrhea, 14 of sterility, 15 of hirsutism, and 7 of pain. The association of acne, obesity, hypertension, and lack of mammary development has received more recent emphasis.[13, 22, 28] The occurrence of menometrorrhagia after long periods of amenorrhea is a frequent observation. Many of the patients are psychically depressed. The presence of the afore-mentioned complex of symptoms in a young woman should suggest careful examination for bilaterally enlarged polycystic ovaries. This finding, in fact, is the necessary criterion for establishment of the diagnosis. The employment of gynecography, as described by Stein,[25] furnishes a ready means of delineating the ovarian pathologic changes, which can be missed readily on even careful bimanual examination, which often is made difficult by the extreme obesity of the patients.

A number of hormone assays have been made on these patients in attempts to focus the diagnosis of the syndrome on a physiologic basis. Preoperative and postoperative studies have been conducted on the urinary excretion of 17-ketosteroids, corticosteroids, and follicle-stimulating hormones by Ingersoll and McDermott,[13] Schnieder and associates,[22] and Jailer and Vande Weile.[15] In general, the values obtained have been within normal ranges.

Treatment.—As already mentioned, the Stein-Leventhal syndrome is characterized by refractoriness to use of hormones. Karnaky[17] apparently succeeded in ridding ovaries of a few cysts using large preoperative doses of stilbestrol, but it is doubtful whether any of his patients were suffering from the complex under consideration. Even cortisone has been disappointing in the treatment of this syndrome, according to Greenblatt.[10] Cyclic therapy with estrogen and stilbestrol has proved efficacious in cases in which response to surgical resection of the ovaries has been borderline. Preoperative management by this means, however, has not produced much beneficial effect. The most widely accepted therapeutic procedure consists of wedge resection of both ovaries, as advocated by Stein and Leventhal.[29] The most recent report of the results of this operation among 88 patients so treated shows the following: (1) accelerated mammary development; (2) resumption of ovulation and menstruation; (3) occurrence of pregnancy in many patients who originally had complained of infertility; (4) increase in the size of uteri that preoperatively were hypoplastic; (5) tendency to disappearance of obesity and acne; and (6) inconstant change in the character of hirsutism, with the hair occasionally becoming of fine texture. Stein postulated that these beneficial effects might be owing to the surgical removal of a mechanical barrier to ovulation.

Pathologic Features.—In earlier writings on this subject, the principal pathologic changes have been ascribed to the ovary.[13, 20, 23, 24, 27, 29] Gross ovarian enlargement, with maintenance of the original shape associated with a remarkable grayish-white pallor, was emphasized. On cut section, a thick

subcapsular fibrous mantle covered a rim of cystic tense immature follicles. This cystic zone in turn overlay an expanded fibrous central core into which cysts did not extend.

The microscopic picture was that of follicular cysts ranging from a primordial stage up to but definitely short of transformation into corpora lutea. Endometrial changes featured for the most part descriptions of proliferative (anovulatory) thickening, sometimes with the development of hyperplasia resembling the pattern of Swiss cheese. Speert,[24] Sommers and coworkers,[23] one of us (Dockerty) and associates,[5] Greenblatt,[10] DeVere and Dempster,[4] and Ernst[8] recently have called attention to the occurrence of endometrial carcinoma as a late complication occurring among patients with this syndrome. The present paper deals especially with this feature.

Materials and Methods

Since the designation "Stein-Leventhal syndrome" did not appear on the clinic records prior to 1940, the problem of finding old cases required considerable screening. Patients with this complex are supposed to be obese, excessively hairy, hypertensive, and infertile. Accordingly, study was made of the records in several hundred cases in which a combination of any three of these conditions occurred. Only those cases were accepted in which typical ovarian lesions were removed for biopsy.

TABLE I. COMPARISON OF CLINICAL DATA IN NONNEOPLASTIC AND NEOPLASTIC GROUPS

DATA	NONNEOPLASTIC (27 PATIENTS)		NEOPLASTIC (16 PATIENTS)	
Marital Status.—				
Married	19		15	
Single	8		1	
Menstruation.—				
Amenorrhea	13	22 (81 per cent)	2	12 (75 per cent)
Menometrorrhagia after amenorrhea	9		9	
Menorrhagia after amenorrhea	0		1	
Menorrhagia	1		1	
Metrorrhagia	1		2	
Menometrorrhagia	1		1	
Normal periods	2		0	
Infertility	19		13	
Hypertension	8		6	
Weight.—				
Obesity	9		12	
Overweight	9		0	
Hirsutism	16		8	

For further augmentation of the series and because previous studies had demonstrated the occurrence of uterine carcinoma as a complication of the Stein-Leventhal syndrome, the files of pathologic specimens were searched for cases missed by the case-record method. Surgical specimens removed from several thousand patients who had endometrial carcinoma have been preserved in toto at the clinic; all of these were examined for the presence of polycystic ovaries. The net result of this double-barreled survey was the discovery of 43 patients who had this syndrome and who had been seen at the clinic from 1909 to 1954, inclusive. Of this total, 16 patients, who are placed in the neoplastic group, had uterine carcinoma. It is to be emphasized that the

only cases of endometrial carcinoma included in this study were those in which the clinical picture was that of the typical Stein-Leventhal syndrome. The remaining 27 patients who did not have this complication, make up the nonneoplastic group. With the material all assembled, the case records were abstracted for pertinent data. All gross pathologic specimens were then restudied. All available slides of tissue were secured and many new ones were made for a final clinicopathologic appraisal of the condition.

Nonneoplastic Group (27 Patients)

Clinical Findings.—Reference to Table I discloses that the various combinations of symptoms and signs originally described by Stein and Leventhal were fairly well borne out in our group of patients.

The ages varied from 17 to 42 years, the greatest number of patients being in the third and fourth decades of life. The age at the time of the menarche did not vary from that of a series of random controls. Menstrual histories prior to development of symptoms brought out several interesting facts. Seven patients originally had experienced normal menstrual function for periods varying from 4 to 7 years. Two other patients related stories of moderate irregularity for 3 or 4 years prior to the onset of trouble. Menses were normal and rhythmic in 2 patients at the time of their admission.

Primary or secondary infertility, a major complaint, is difficult to appraise inasmuch as 8 of our 27 patients were single. Eight patients had been pregnant prior to treatment at the clinic. Only one patient had multiple viable offspring. Pregnancy in one had ended in a miscarriage. The time of confinement in 3 patients was 8, 7, and 5 years, respectively, prior to their registration at the clinic. The dates of confinement in the remaining 3 patients were not available from the record but in none were they recent.

Hirsutism was recorded as being present in 16 of the 27 patients. It is highly possible, however, that attention was not paid to lesser degrees of hirsutism, since some of the patients had been seen prior to recognition of the Stein-Leventhal syndrome. Manifest obesity was present in 9 patients and an additional 9 patients were overweight on the basis of height-weight calculations. Thus, two thirds were of more than normal weight.

Nothing of pertinence with reference to mammary development was discovered from the records in our cases. The blood pressure was increased minimally in 8 patients if a systolic pressure of 130 mm. of mercury is considered to represent the upper limit of normal.

Of several patients in whom the basal metabolic rate was determined, only one had abnormal results (–50 per cent); this patient had the Stein-Leventhal syndrome complicated by pelvic tuberculosis.

Studies of the urinary excretion of 17-ketosteroids in 11 patients and estimations of the urinary content of corticosteroid substances (5 patients), of estrogen (5 patients) and of pituitary gonadotropins (3 patients) all failed to disclose abnormal amounts of these substances.

Treatment.—The principal type of treatment employed in these 27 patients was surgical. In 19 patients, this consisted of removal of bilateral ovarian wedges designed to include the thickened tunica and a generous portion of the deeper ovarian stroma. One of these 19 patients also had a plastic procedure done on the left tube. The amount of ovarian tissue sacrificed amounted to approximately one third of each ovary and it included the zone of polycystic change to be described later. The ensuing raw surfaces were approximated with a row of running sutures of fine chromic catgut on an atraumatic needle. Two of the remaining 8 patients underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy because of associate fibroids.

One patient had resection of her one "remaining" ovary. One patient, who was also suffering from associated pelvic tuberculosis, had bilateral salpingo-oophorectomy. Four patients, seen many years ago, underwent bilateral oophorectomy.

Ancillary therapy given in 2 instances included preoperative use of cortisone and corticotropin (ACTH). These agents appeared to have no effect on the complaints.

Follow-up Studies.—To date there has been no instance of clinically palpable recurrence of polycystic ovaries in this group.

Effect on fertility: Since 8 patients were unmarried and since ablative ovarian operations had been performed on 3, there remained 19 patients in whom therapeutic effects could be appraised in terms of fertility. Five of these 19 (26 per cent) have reported subsequent pregnancies, for a total of five full-term deliveries. A sixth patient currently is pregnant. No abortions were reported in this group.

Menstrual function: Three recently observed patients and the 3 whose ovaries had been removed are deleted from analysis pertaining to menstrual function. Of the remaining 21, a total of 16 (76 per cent) have resumed normal menstrual rhythm. In one of these patients who had a long history of amenorrhea, a presumably normal period ensued on the sixth day after operation. Two of the remaining 5 patients required cyclic therapy with estrogen and progesterone to maintain menstrual regularity. The other 3 patients have not experienced relief from their preoperative menstrual difficulties.

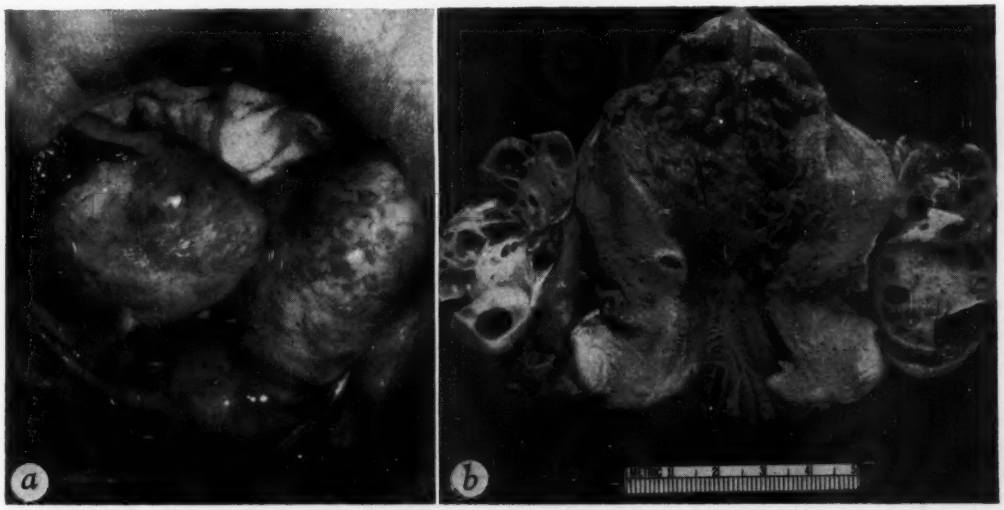


Fig. 1.—*a*, Bilateral polycystic ovaries in situ in a patient with the Stein-Leventhal syndrome. Note relation of size of ovary and uterus. The pale "oyster" appearance of the ovaries contrasts with the relatively dark appearance of the tubes and uterine fundus. *b*, Bilateral polycystic ovaries and diffuse polypoid endometrial adenocarcinoma. This combination was noted among 16 of the 43 patients with the syndrome.

Hirsutism: None of the 16 patients who complained of this symptom achieved complete relief. However, about 60 per cent of the patients reported thinning of the excessive hair, along with lightening of its color and texture.

Obesity: Six patients lost weight. It is difficult to state whether the reduction in weight observed in these patients was effected through operative correction of the ovarian lesions or through the medium of "reduction diets." Five patients were unchanged as to obesity. Data concerning weight were unavailable in the others.

Gross Pathologic Findings.—The ovaries were enlarged bilaterally and more or less symmetrically. In fresh specimens and as viewed at operation, a characteristic pale, opalescent "oyster-colored" appearance was manifest. The weights of whole ovaries, like their size, sometimes exceeded five times that of the normal.

Sections made by cutting exposed a surface-mantling rind of tough grayish-white tissue that measured up to 4 or 5 mm. in thickness. Underneath this lay a zone in which the tissue was almost replaced by cysts averaging 5 mm. in diameter and rarely measuring more than 2 cm. in width (Fig. 1). These cysts were filled regularly with clear fluid that appeared to be under definite tension. The cysts rarely were collapsed. Large hemorrhagic follicular cysts were not observed; mature or degenerating corpora lutea were conspicuous by their virtual absence. The subcortical and medullary zones of the ovaries appeared rather fibrous and edematous without evidence of formation of cysts. The uteri did not appear to be remarkable. The endometrium available for examination, either as a curetted specimen or as obtained at hysterectomy, was thickened in 13 cases and rather atrophic in 2.



Fig. 2.—Typical appearance of ovarian specimen removed by wedge resection. Note the thick cortical rind, the immediately subjacent ring of closely crowded small follicular cysts, the absence of corpora lutea, and the wide central cyst-free expanse of fibrous ovarian stroma.

Microscopic Changes.—A fibrous and, at times, a hyaline investment that encompassed the width of several high-power microscopic fields was found just underneath the germinal epithelium (Fig. 2). In the deeper portions of this layer, and in the tissues separating the follicular cysts, were large numbers of primordial ova and primordial follicles. As many as 20 to 30 of these structures were observed in certain microscopic fields viewed with the low-power objective. Large numbers of diminutive maturing follicles occurred just beneath the peripheral cirrhotic zone; these follicles rarely reached a size sufficient to effect notable bulging of the ovarian surface (Fig. 3, *a*). Few of them actually had reached a size or a degree of maturity seen in the ordinary follicular cysts. The inner lining was composed of granulosa frequently thinned out to several layers only. Surrounding these immature follicles was a remarkable proliferation and piling up of the theca interna that here and there appeared to show transition from oval cells to rounded granulosa-like elements. Stains for fat frequently demonstrated the presence of lipoid droplets but maturation into corpora lutea was rare. Mitotic figures

were present not infrequently in the proliferating theca interna (Fig. 3, *b*). Only rarely did the follicles extend into the central cortical and medullary zones (Fig. 4). Numerous atretic follicles were observed in these ovarian specimens, and the presence of an occasional well-formed corpus albicans indicated previous normal ovarian function.

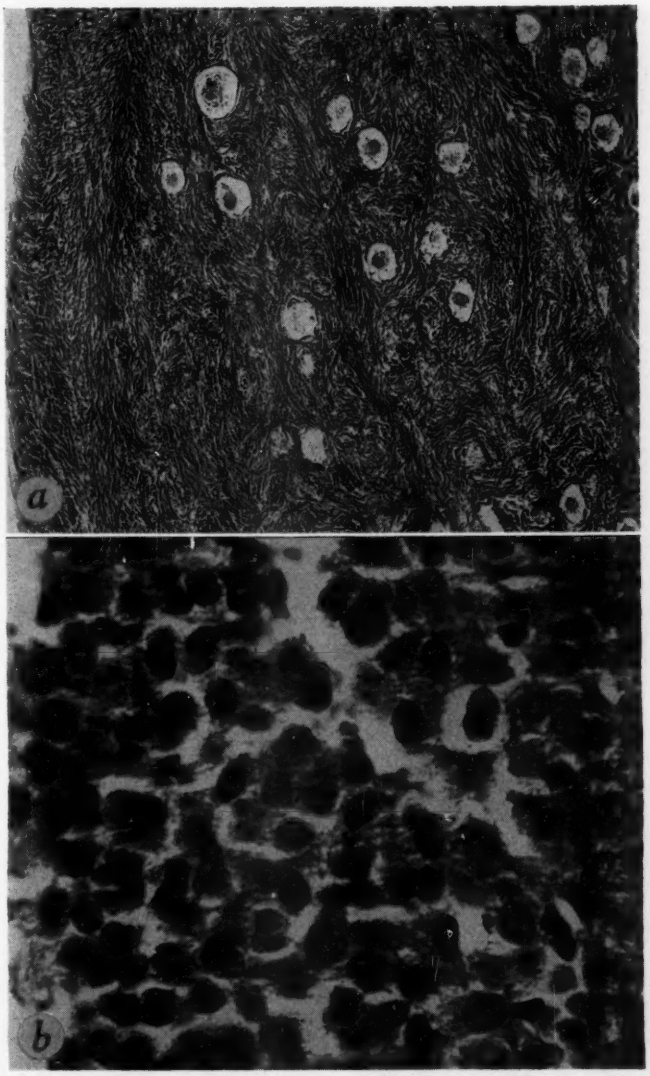


Fig. 3.—*a*, "Stein-Leventhal ovary" featuring cortical fibrous thickening and clusters of primordial ova and follicles. Frequency of occurrence of these last-named clusters has not received merited attention. (Hematoxylin and eosin; ×110.) *b*, Lining of one of the cysts in the same ovary, showing hyperplastic theca interna; note the mitotic figure. (Hematoxylin and eosin; ×740.)

The various ovarian and endometrial changes were graded with reference to degrees of severity (Table II).

Neoplastic Group (16 Patients)

As indicated, this category included patients who exhibited the clinical features of the Stein-Leventhal syndrome but in whom endometrial carcinoma

also was discovered (Fig. 1, *b*). The clinical features of this group did not differ sufficiently from those of the nonneoplastic category to warrant detailed separate analysis. Reference to Table I shows the similarities.

TABLE II. COMPARISON OF PATHOLOGIC FEATURES IN NONNEOPLASTIC AND NEOPLASTIC GROUPS

CHANGE	NONNEOPLASTIC (27 PATIENTS)		NEOPLASTIC (16 PATIENTS)	
Endometrium	Hyperplasia	2	Adenocarcinoma	12
	Atrophy	2	Grade I	8
	Proliferation	11	Grade II	2
			Grade III	2
			Adenoacanthoma	3
			Grade I	1
			Grade II	2
			Mesodermal mixed tumor	1
Ovarian Fibrosis (Cortical Rind).—				
Grade I	1		1	
Grade II	16		8	
Grade III	10		6	
Grade IV	0		1	
Hyperplasia of Theca Interna.—				
Grade I	14		3	
Grade II	13		12	
Grade III	0		1	
Follicular Cysts.—				
Grade I	4		2	
Grade II	14		8	
Grade III	9		6	
Primordial ova	26		13	
Ovarian hilus	No change		Sertoli-like cells	4
			Leydig-like cells	5

Some differences between the groups were apparent. The patients in the neoplastic group were somewhat older. The ages ranged from 27 to 48 years, with the majority of patients in their late thirties and forties. It is considered that endometrial carcinoma is best considered as a late complication of the unsuccessfully treated syndrome. Yet it is surprising, in view of the expected occurrence of endometrial carcinoma in older women (96 per cent are more than 40 years of age), that so many of these patients were young women. The incidence of long periods of amenorrhea was in keeping with that observed in the nonneoplastic group, and two of the patients presented endometrial growths of such diminutive size that bleeding and discharge had not yet occurred. In the remaining 14 patients, however, abnormal bleeding was manifest. Performance of dilatation and curettage never should be omitted in appraising the status of a patient with the Stein-Leventhal syndrome. The somewhat greater incidence of hypertension and of obesity in the neoplastic group may reflect an older age of the patients or a longer duration of the syndrome. Only one viable offspring had been born in this group of 16 women, of whom 15 were married; 13 of the 15 had noted complete infertility.

Treatment and Results.—Treatment in the neoplastic group consisted of dilatation and curettage followed by immediate hysterectomy and salpingo-oophorectomy on the pathologic discovery of coexisting endometrial adenocarcinoma. The resultant changes in the degrees of hirsutism and obesity paralleled those already described for patients in the nonneoplastic group. All of the patients except 2 were living and well at the time of the present report; the causes of death in these 2 remain uncertain since necropsies were not performed.

Pathologic Features.—These findings are listed in Table II, which shows the similarities between this group and the nonneoplastic category. Some differences of possible significance were noted. The ovaries were perhaps more cystic in the neoplastic group and the average size of the cysts was somewhat greater, diameters up to 2.5 cm. being observed. Primordial ova in this group were reduced in numbers as compared with those in the nonneoplastic group, and none whatsoever were found in 3 of the ovaries examined.

Hilar sections disclosed the presence of tubular structures in 4 patients. These were lined by Sertoli-like cells, each with an oval nucleus and a prominent nucleolus (Fig. 5, *a*). Clusters of lipid-laden Leydig-like cells with large spherical nuclei (sometimes doubly nucleated) were observed in 5 specimens (Fig.

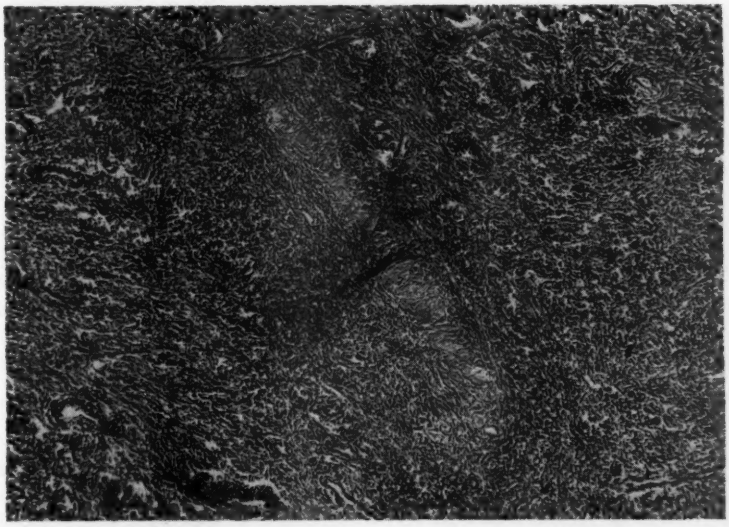


Fig. 4.—Section from the deep cortical cyst-free zone in one of these large ovaries; note the degree of fibrosis. (Hematoxylin and eosin; ×110.)

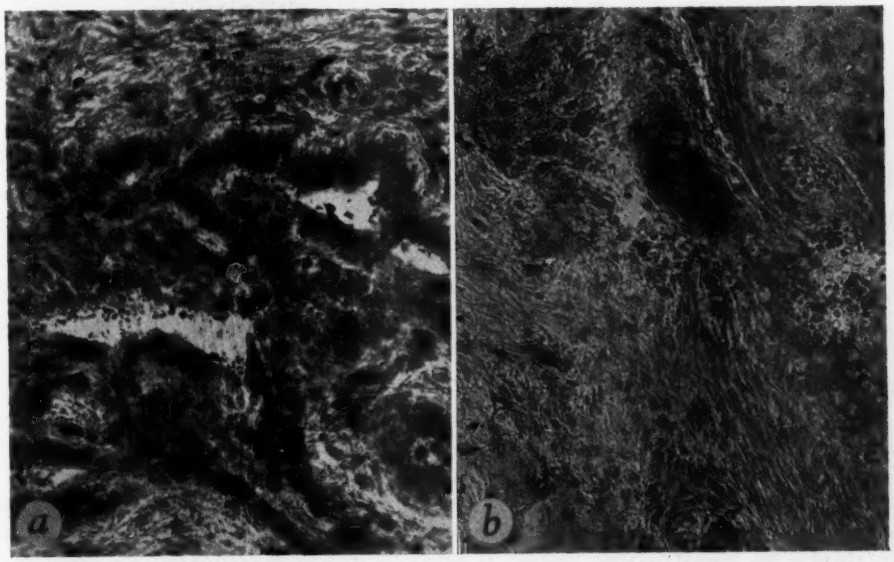


Fig. 5.—Ovaries in the Stein-Leventhal syndrome associated with endometrial carcinoma. *a*, Ovarian hilar nests of Sertoli-like cells lining tubules. (Hematoxylin and eosin; ×200.) *b*, Ovarian hilar nests of Leydig-like cells. (Sudan III; ×200.)

5, *b*). These hilar findings may not represent group differences, since the ovarian wedging performed therapeutically in the nonneoplastic group was not productive of hilar tissue.

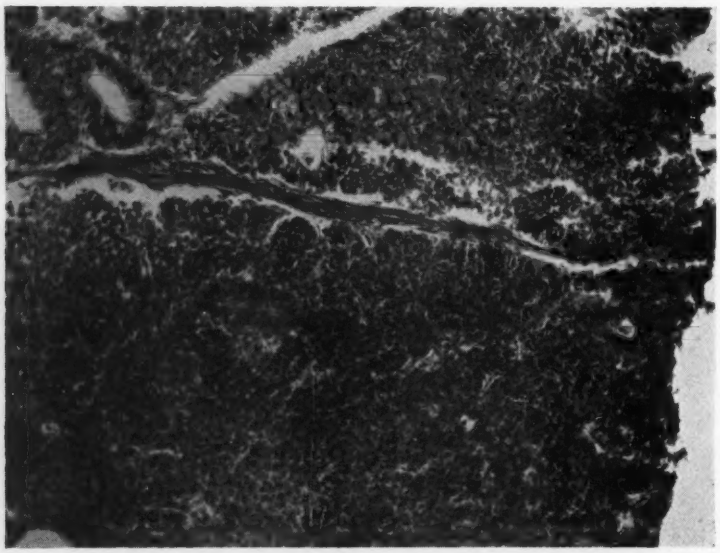


Fig. 6.—Adenocarcinoma, Grade II, of endometrium with anaplastic cells and a back-to-back arrangement of poorly differentiated glandlike structures. From the endometrium shown grossly in Fig. 1, *a*. (Hematoxylin and eosin; ×100.)

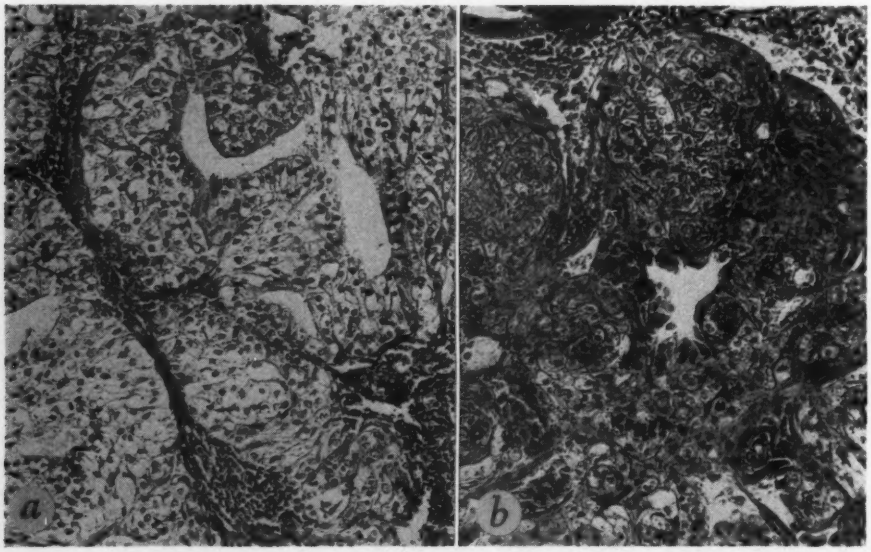


Fig. 7.—Adenoacanthoma, Grade I, in a patient with uterine carcinoma and typical Stein-Leventhal syndrome. *a*, Glandular components. *b*, Squamous components. (Both hematoxylin and eosin; ×150.)

The uterine carcinomas were diffuse in 4 cases, whereas they apparently were circumscribed malignant adenomas in the remainder. In none was there much depth of penetration (Figs. 6 and 7). Twelve of the 16 were adenocarcinomas and 3 were adenoacanthomas; the remaining lesion was an adenocarcinoma with regions of malignant metaplasia of the stroma featuring production of osteoid.

Comment

Although the syndrome under discussion is relatively uncommon, Stein recently has been able to report on a personal series of 88 patients treated by means of wedge resection of the ovaries. The series of Meaker[19] (65 cases) and of Ingersoll and McDermott[13] (29 cases) are sizable. It is our opinion that more and more cases will come to light with growing recognition of the Stein-Leventhal symptom complex. A considerable amount of searching was required before our series of 43 cases was assembled out of a miscellany of clinical and pathologic diagnoses. It is suggested that a similar search by others will be comparably rewarding.

Our study adds no pertinent evidence to support or disprove the three current theories regarding the etiological factors, namely, pituitary hypersecretion,[29] deficiency of luteinizing hormone,[11] and distortion of the ovarian spiral arteries.[21] In our neoplastic category, a total of 9 cases exhibited ovarian hilar rests consisting of Sertoli-like cells or Leydig-like cells or both. Benson and co-workers[2] observed these rests in the hili of normal ovaries and we have noted them in a control series. Geist and Gaines[9] have reported luteinization of the theca cells as being suggestive of increased gonadotropic stimulation. The ovaries that we studied exhibited pronounced hyperplasia of the theca interna but no great tendency toward luteinization. We were impressed with the apparent tendency of large numbers of follicles to proceed along the lines of ripening without being able to achieve maturation. Whether the cystic degenerative changes resulted in overcrowding of the ovary, with secondary alterations in the vasculature and nutrition of the cortex leading to fibrosis, could not be determined in our series.

While it is obvious from the experiments of Van Wagenen and Morse[31] that mere resection of one third of the ovarian cortex should not deplete ovarian function, it is perhaps more difficult to understand why such an operation gives relief from the syndrome under discussion. Perhaps reduction of the ovarian "target area" promotes better pituitary-ovarian hormonal balance, as expressed by the views of Bailey,[1] Stein and Leventhal,[29] and Novak,[18] as applying to Lipschutz's "law of follicular constancy." Perhaps ovarian resection breaks the fibrous barrier or relieves increased intraovarian pressure, thus improving the venous and arterial supply of follicles in a state of arrested maturation. Such a theory has been favored by Hirsch,[12] Jacobsen[14] and Reynolds.[21]

We have had no experience with the use of stilbestrol in treating this condition. Karnaky[17] considered it to be of value. The employment of cyclic therapy with estrogen and progesterone had been unsuccessful in most of our patients. Two of our patients received cortisone with essentially no effect on their symptom complex, although Greenblatt,[10] as well as Jones and associates,[16] noted some beneficial effect from its use.

Perhaps our most important observation in connection with the Stein-Leventhal syndrome concerns the complication of endometrial carcinoma, which appears to develop in neglected cases with long histories of trouble. Our interest in this association stemmed from a paper by Speert[24] who, in 1949, reported on several young women with endometrial carcinoma who were suffering

from the effects of this symptom complex. In a comparable series reported by one of us (Dockerty) and associates,[5] almost 20 per cent of women less than 40 years of age who had carcinoma of the uterus gave clinical evidence of the Stein-Leventhal syndrome. Sommers and co-workers,[23] Greenblatt,[10] DeVere and Dempster,[4] and Ernst[8] likewise have reported this association. That the relationship is much more than coincidental is evidenced by the fact that 16 of our 43 patients had malignant endometrial lesions. It might be well to follow closely patients on whom bilateral wedge resection of the ovary has been performed to ascertain whether this operation prevents fruition of this carcinogenic tendency.

It has been emphasized by one of us (Dockerty) and Mussey[6] that granulosal-cell tumors of the ovary are carcinogenic with regard to the endometrium. It could be postulated that the hyperplastic theca interna observed in the ovaries of patients with the Stein-Leventhal syndrome, through elaboration of excessive amounts of estrogen or through uninterrupted elaboration of normal amounts, could have a comparable effect.

Summary and Conclusions

A study has been made at the Mayo Clinic of the clinical and pathologic data on 43 patients who had the Stein-Leventhal syndrome. The majority of these patients were obese, excessively hairy, hypertensive, and infertile. Menstrual irregularities featuring a high incidence of amennorrhea were extremely common.

Characteristic ovarian changes consisted of bilateral enlargement, thick cortical rinds, and polycystic cortices. The cysts represented maturing follicles that were tense with fluid and lined by granulosa cells. The surrounding theca was hyperplastic and sometimes fatty. Numerous primordial ova and follicles were usually apparent. The central portions of the ovaries were tough and fibrous. Corpora lutea were nearly always absent.

Surgical resection of a wedge from the ovaries was curative in those patients who did not have malignant lesions of the endometrium and who were left with ovarian remnants.

Sixteen of the 43 patients had the associated complication of endometrial carcinoma. It is not considered that carcinoma in these cases is merely coincidental. The finding of Sertoli-like and Leydig-like elements in the ovarian hili in 9 of these 16 patients may or may not be of significance in this connection.

Patients suffering from the effects of the syndrome should undergo dilatation and curettage prior to definitive surgical attack on the ovaries. The effect of ovarian resection on possible prevention of uterine malignant lesions in these cases should be appraised further.

Addendum.—While this paper was being prepared, we encountered two additional patients who had the Stein-Leventhal syndrome. A 36-year-old woman had Grade I endometrial adenoacanthoma along with typical polycystic ovaries. In the second instance, the patient, a candidate for the nonneoplastic category, was treated by wedge resection of the ovary. Data from these patients are not compiled in the main body of this paper. This brings to 45 the number of patients observed, including 17 with associated uterine carcinoma.

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RESISTANT TRICHOMONIASIS IN THE FEMALE*

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EVERY physician who treats women is plagued with patients with resistant and recurrent trichomoniasis. The factors responsible for the resistance to therapy and the recurrences after successful treatments are not always clear. Perhaps if we could find the few missing links in the etiology and the life cycle of the Trichomonas our understanding would be more complete. We believe that trichomoniasis is more common in women than in men and that the infection is frequently transmitted by sexual intercourse. The disease may be asymptomatic and both men and women can be carriers. Exacerbations could be precipitated in part by a change in the accompanying bacterial flora.

Fifty per cent of the vaginal discharges in women harbor *Trichomonas vaginalis*. Recent reports on nonspecific male infections harboring Trichomonas show incidences of 12 to 15 per cent.[3] At times the Trichomonas are difficult to find and can easily be overlooked, particularly in the male, when wet smears of the urethral and prostatic secretions are not routinely utilized. In other words, the actual incidence of male trichomoniasis may be larger than is now ordinarily believed or recognized.

The object of presenting this paper is to report our treatment experiences in 40 cases of vaginal and urinary trichomoniasis in which the urinary tract appeared to be the primary resistant focus. The common involvement of the urinary tract has been known and previously reported by Allen,[1] Hesseltine,[5] and others. Allen and Heckel studied 43 women cystoscopically and noted that the inflammatory changes were limited to the vesical neck and urethra.

Trichomonas have been recovered from many orificial organs of the body including the vagina, uterus, tubes, Bartholin's and Skene's glands, urethra, bladder, prostate, kidneys, mouth, and intestines. Bernstine and Rakoff[2] recognized Trichomonas in the urinary tract as secondary invaders in one-third of their cases and their treatments included urethral instillations. Sar-Louis[15] suggested urethral treatments with a blower and magnesium trisilicate parasitical powder. He regarded the urethra as a focus and its eradication prevented recurrences.

In August, 1955, Kean[6] stated that trichomoniasis may be primary in the urethra but that the dual involvement was imperfectly understood. He found vaginal trichomoniasis and *B. coli* cystitis frequent companions and suggested that the bacteria rode up the urethra on the backs of the Trichomonas.

Our understanding of this dual involvement in women is based on our experiences in observing trichomoniasis in men. My observations in the male date

*Presented at a meeting of the Chicago Gynecological Society, Dec. 16, 1955.

back to 1928 when I reported the first 2 cases on record of Trichomonas prostatovesiculitis. We have found a damaged and strictural male urethra very vulnerable to Trichomonas (12 per cent). The cases we are now reporting showed chronic urethral foci with lowered local resistance to infection and Trichomonas invasion. The eradication of these urethral foci has resulted in the clearing of the urinary and vaginal trichomoniasis.

Material

We have examined 43 patients with chronic urinary and vaginal trichomoniasis, of whom only 40 were treated, 2 in the office and 38 in the hospital with office follow-up. The 2 office-treated cases failed to clear after one year's treatment. One patient did not return for hospitalization and the other had a hysterectomy and failed to return.

Of the 40 patients, all were white, 22 were married, 13 were single, and 5 were divorced, widowed, or separated. Twenty of these women had been pregnant, borne 26 children, and 6 had had abortions. Twenty (50 per cent) were menstruating while 20 were menopausal (18 by hysterectomy). The youngest patient was 19, the oldest 76, with an average age of 40 years.

Data on the Series of 40 Women

Symptoms.—The duration of symptoms varied from 1 to 18 years, with an average of 4.8 years. From the urinary tract, 22 women had frequency, 20 burning, 15 urgency, and 18 nocturia. Nine of 40 women gave a history of gross hematuria. Vaginally, 14 women complained of itching; 37 had a discharge while 3 had none. Three patients gave a history of Trichomonas vaginitis. Motile Trichomonas were found in the 37 women with a vaginal discharge. Six patients complained of incontinence (4 had stress and strain and 2 urgency).

Physical and Urine Examinations.—The examination of the abdomen was negative in 32 women. There was localized or diffuse tenderness in 8. Palpation of the urethra disclosed thickening in 30, tenderness in 6, discharge in 1, and visible caruncles in 3. Skene's ducts were found thickened in 35 urethras while 5 seemed normal. Stripping of the distal urethra and Skene's ducts in 35 examinations revealed motile Trichomonas in 19 (54 per cent).

The voided urine specimens showed that 27 had no red cells, 9 had 0-10, 2 had 10-20, and 2 had 100 or more per high-power field. Twenty-four specimens had 0-10 pus cells, 10 had 10-20, 1 had 40-50, while only 4 had many pus cells per high-power field. Motile Trichomonas were found in the 40 urines (32 in the hospital and 40 in the office). Two patients had residual urine (one 500 and the other 200 c.c.). Thirty-nine urine specimens were cultured and 11 showed a single-organism infection, while 13 showed a mixed infection. Fifteen urine cultures (37 per cent) showed no growth. A breakdown of the positive cultures showed that the *Staphylococcus albus* was found in 14 specimens, *B. coli* in 10, streptococci in 5, *Aerobacter aerogenes* in 3, Proteus in 2, and Alkaligenes in 1.

Cystoscopy-Urethroscopy.—Thirty-eight patients were cystourethroscoped in the hospital under caudal block and intravenous Pentothal sodium anesthesia. The McCarthy panendoscope or resectoscope was used for the examinations and treatments. Fourteen patients had precystoscopic intravenous pyelograms. Five patients had hydronephrosis, of whom 2 required surgical correction and 3 ureteral dilatation. Two patients had a solitary kidney. Eight cystograms disclosed bladder hypertrophy, 4 with residual urine.

Cystoscopy showed a normal bladder mucosa in 37 patients; mild hyperemia occurred in 14 of these. One nonspecific bladder ulcer was recorded. The bladder wall seemed hypertrophied in 9 patients, the bladder neck inflamed in 2 and fibrosed in 9. Hyperemia of the trigone was noted 27 times; in 11 of

these the trigone was covered with an irregular whitish membrane. It was thickened and elevated on 3 occasions. The following urethral lesions were noted in 38 patients: granulations (soft and hard) 27, mucosal cysts 10, polyps 4, sclerosis 4, hyperemia 1, contracted external meatus 4, and normal urethra 2.

Treatments.—Forty patients had previous vaginal treatments. Eleven had urethral therapy consisting of instillations, dilatations, and antibiotics. In one-half (50 per cent) of these patients the symptoms persisted and the others were plagued with recurrences.

Our treatments consisted of removing all urinary foci which could possibly serve as primary concentration points for Trichomonas. Following preliminary excretory pyelograms, a combined urethrocystoscopic examination and treatments were routinely carried out. The treatments consisted of 19 urethral fulgurations (including fulguration of the trigone in 11), 11 urethral fulgurations with transurethral removal of deep urethral and vesical neck tissues, and transurethral resection only in 8. In 34 patients Skene's ducts were catheterized with an illuminated speculum and a blunt probe. Electrosurgical incision into the lumen of the urethra destroyed these ducts as a focus of infection. In 11 urethras, 1 or more supernumerary ducts were found; one patient had 7. A meatotomy incision was made when the meatus was small or contracted. Meatal polyps and caruncles were removed. All caruncle tissue was biopsied. Following the operation a 22 or 24 F. Malecot or Foley catheter was left in situ for 48 to 72 hours.

Postoperative Care.—Dihydrostreptomycin and penicillin were given intramuscularly twice daily while the catheter was in place. Oral medication was substituted on the third and fourth days. Sensitivity tests were used to aid in selecting the drug of choice. For the nervous woman oral phenobarbital was given morning and evening. Following the removal of the catheter, patients were ambulated and allowed to take sitz baths once or twice daily. Some patients had little postoperative discomfort while in others the dysuria was intermittently severe. It takes approximately 4 to 6 weeks for the urethra to heal. The healing is expedited by the use of antibiotics. After the healing is complete and the urine is clear, the urethra is calibrated and dilated once or twice if necessary. Previously prescribed vaginal treatments are resumed at home and continued while the urethra is under observation and treatment.

Postoperative Complications.—The treatment complications have been few and were not troublesome. The disadvantages are 4 to 6 days of hospitalization and 4 to 6 weeks' postoperative morbidity. Patients with stress and strain incontinence may be made slightly worse due to loss of the urethral spasm. Temporary postoperative incontinence was noted in 3 patients which lasted from 4 to 12 weeks. One patient developed a soft urethral stricture in the resected area which yielded to dilatation. One patient had gross bleeding from an incised Skene's duct but this was easily controlled by a pressure dressing and an ice pack. A late bladder hemorrhage has not occurred but it could easily happen. Readmission is another disadvantage of our treatment regimen, usually resulting from incomplete eradication of all urethral foci. Five patients were admitted twice for treatment while 3 others were admitted 3 times. In other words, 8 patients (21 per cent) required 2 or more hospital admissions and treatments to obtain a negative result. Our records show that the 8 re-treated patients remained well except for 1 who had a temporary recurrence after one year. Further studies indicate that 7 of the 8 readmitted patients had anomalous supernumerary paraurethral ducts. In our opinion anomalous ducts predispose to persistent trichomoniasis. The detection and destruction of all of these anomalous ducts constitute by far the most difficult problem to overcome in the treatment of this group of patients.

Results.—Our results have been surprisingly good. In the follow-up period the Trichomonas seem to disappear after 30 to 90 days, along with the pus and

red cells in the urine. Thirty-two out of 40 patients (80 per cent) seemingly were cleared of urinary and vaginal trichomoniasis. Four (10 per cent) cleared patients had temporary recurrences after 1 to 2 years. They again became negative following a short course of urinary and vaginal re-treatments. Two treatment failures were noted after 1 year's office treatment. These patients should have received hospital treatment. Six (15 per cent) hospital patients had insufficient office follow-up to record the end results although 2 (5 per cent) appeared to have been cleared. To our knowledge there was no patient who was made permanently worse following the above urethral treatments. All of these patients except 4 have been treated since January, 1948. Extended posttreatment follow-up in the majority of patients has been in the hands of the referring physician. There may have been more recurrences which have not been brought to our attention.

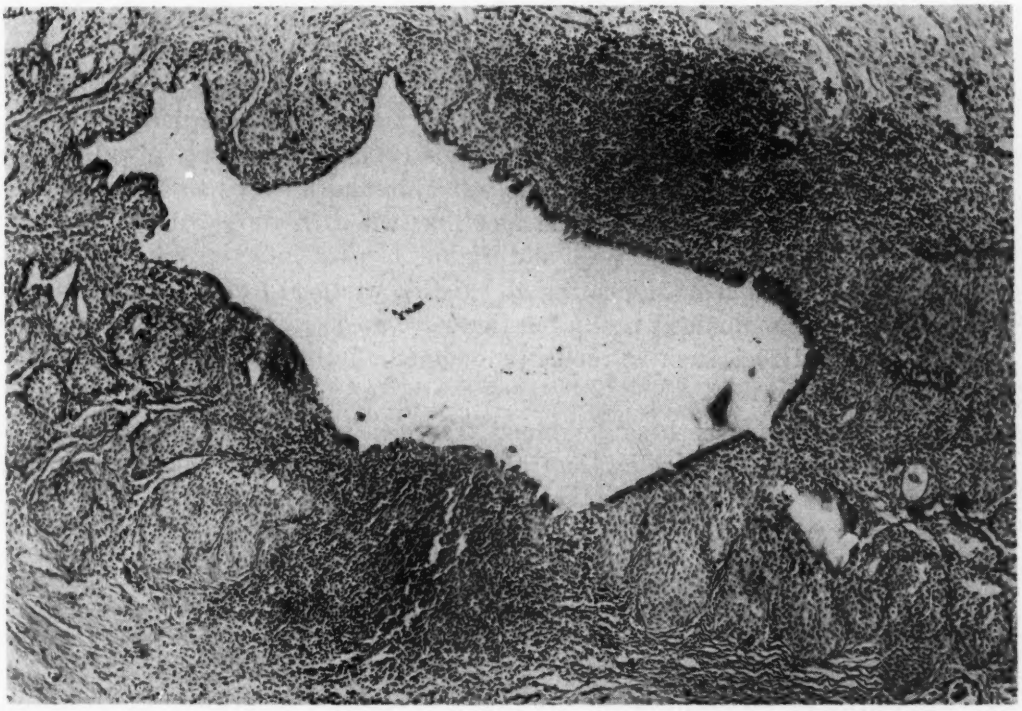


Fig. 1.—Tissue section shows grouped lymphocytic infiltration, metaplasia of glandular tissue from transitional to squamous epithelium, and nonspecific inflammation. (×130; reduced ⅙.)

Pathology.—We have the microscopic tissue examinations of 11 patients who were operated upon. They all show evidence of chronic infection (Fig. 1). Seven tissue sections show definite evidence of vesical neck fibrosis; 3 show muscular hypertrophy and fibrosis, and in one there were tissue changes compatible with a diagnosis of chronic cystitis. In no instance have we been able to demonstrate the Trichomonas in the tissue sections. Our laboratory technician, Miss Mary McNichols, at one time showed me a large group of Trichomonas (150 or more) expressed from a Skene's duct. We interpreted this finding as evidence of a Skene's gland focus of Trichomonas.

Comment

Our observations concerning these 40 patients are not conclusive but they are very suggestive that these resistant and recurrent cases may harbor a primary urinary and urethral focus. Other investigators (Reich,[8] Shelanski and

Savitz,[16] and others) have noted urethral, urinary, and vaginal involvement but no definite urinary therapy has been recommended. Included in this paper are 3 cases previously reported in 1948 which strongly suggested the urethra, Skene or Bartholin gland involvement as the primary Trichomonas focus.

Many factors of human trichomoniasis remain obscure. Both men and women are afflicted with Trichomonas. Sexual intercourse is one common avenue for their dissemination. Sexual relations may well account for the recurrences after treatment. Previous studies do not favor rectal or oral contamination as etiological factors. The infection is probably more widespread in men than is now believed and this could be one major factor in dissemination in women. Observations in the male show that a devitalized, strictured urethra is susceptible to *Trichomonas vaginalis*. Our studies in the female suggest that chronic female urethritis and skeneitis result in low tissue resistance to infection and Trichomonas invasion. The large percentage of negative urinary cultures which was found in this series would indicate that the Trichomonas is not a carrier of bacteria but rather a secondary invader after the soil has been prepared by chronic infection and lowered tissue resistance. This view is supported also by the fact that when the infected urethral foci are destroyed, the new tissues are better able to resist infections and recurrent Trichomonas invasion. Eradicating all existing urethral foci will clear urinary and vaginal trichomoniasis providing there are no coexisting vaginal foci. All chronic vaginal foci, such as cervicitis or bartholinitis, should be removed by surgical treatment.

In our experience these combined treatments offer these chronically ill patients more permanent relief than any treatments which have been previously suggested. To my knowledge, there is no oral or local medication which will permanently relieve these patients of resistant trichomoniasis.

Conclusions

1. Forty patients with urinary and vaginal trichomoniasis are reported. Thirty-eight were treated by urethral surgery and 2 in the office.

2. Surgical treatment of the urethral foci resulted in clearing the resistant and recurrent trichomoniasis in 32 patients (80 per cent).

3. Eradication of all urethral and vaginal foci is necessary for the permanent clearance of resistant female trichomoniasis.

4. Anomalies of the distal urethra are common. Surgical removal of all anomalous paraurethral ducts is technically a difficult procedure.

5. In 7 of our 8 patients who were readmitted additional anomalous ducts were found and their treatment resulted in clearing the trichomoniasis.

6. Through normal sexual intercourse the Trichomonas are frequently transferred from the male to the female or vice versa.

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Discussion

DR. JOHN W. HUFFMAN.—The management of intractable trichomoniasis is a difficult and frustrating problem. Coital reinfection explains the difficulty in curing some cases. Failure to continue treatment after one negative vaginal smear explains others.

From my experience persistent urethral foci harboring trichomonads are a source of vaginal reinfection in relatively few women.

Like their homologue, the prostate, the paraurethral ducts and glands lying about the female urethra offer an excellent nesting place for organisms from the vagina. Ordinarily the urethral labia protect the urethra from contamination with vaginal secretions. During coitus and cleansing, however, infectious material may gain access to the urethral canal.

After reading the essayist's paper, I took from my office files the records of 50 consecutive cases of intractable vaginal trichomoniasis. I sought for a common denominator in them. All except one patient had associated pelvic pathology. Thirty of the patients had clinical chronic cervicitis. Two had very extensive endometriosis, 6 had residues of pelvic infection, 2 were associated with recurrent dysfunctional uterine bleeding, 3 had chronic atrophic vaginitis. One patient had a foreign body and another had vaginal granulation tissue. Seven suffered from intractable trichomoniasis with mycotic infections between the episodes of trichomoniasis. Six cases of the 50 reviewed had some type of urinary tract pathology. Each of these 6 cases was combined with some type of genital pathology.

Cases of intractable Trichomonas vaginitis are encountered which persist despite prolonged intensive and thorough vaginal treatment and despite the elimination of consort reinfection. In view of this and after considering the cases I have mentioned it seems logical to assume that the trichomonads persist when they become implanted in chronically diseased tissues.

If a urethral focus can be demonstrated, Dr. Riba's approach to the problem seems, from the reported results, to offer much needed help. I wonder, however, whether Dr. Riba gains his effect from eradicating unhealthy urethral tissues which afford the trichomonads a friendly environment or whether the trichomonads produce the urethral inflammation.

DR. RIBA (Closing).—I appreciate Dr. Huffman's discussion. At the present time I feel that we perhaps know very little about this subject. Our experience so far only allows us to draw some premature conclusions. This report should be a steppingstone for future studies.

In answer to Dr. Huffman's question, my impression is that there are chronic inflammatory lesions present in the urinary tract and that the lowered resistance predisposes to Trichomonas invasion. After the invasion it is impossible to eradicate the Trichomonas in these patients until the chronic inflammatory foci (urinary and vaginal) have been destroyed. The replacement tissues seemingly are not as vulnerable to the Trichomonas invasion and infection.

THE CHALLENGE OF COMPREHENSIVE GYNECOLOGY*

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THE title chosen for this paper indicates a point of view neither clearly defined nor widely accepted. Yet there is a need, from time to time, for a specialist to sit back, draw a breath, and give consideration to the broad aims of his chosen field, and its place and responsibilities in maintaining the nation's health. This report is a personal evaluation, then, of some principles that appear to be important in the practice of gynecology, as well as a critical look at some illustrative case material, and an earnest plea for the basic ingredients that need to be introduced into our training programs in order to provide the country with competent and complete gynecologic care for future years.

Comprehensive gynecology is a term we may use to signify the science of treating all difficulties and diseases peculiar to women. In the last fifty years, tremendous strides have been made in basic disciplines that were little understood or nonexistent before 1900. In the nineteenth century, for instance, modern obstetrics was only emerging from the period of midwifery, therapeutic radiation was unknown, endocrine interrelationships unappreciated, and psychiatry an infant science almost exclusively involved in the diagnosis of the abnormal.

With the development of knowledge in these and other areas of technologic advance, and its application to the broad area of surgery, it was inevitable that the field of gynecology, like other specialties, became splintered into various compartments handled by those competent to deal in one or another of the several newer aspects of women's diseases. As a result there are many endocrinologists today who still must rely on surgical associates to do a pelvic examination. Those with exclusive training in obstetrics may often feel inadequately trained to deal with advanced endometriosis or pelvic carcinoma. Psychiatrists have at times discovered too late an organic basis for symptoms they believed due, perhaps, to a maladjusted adolescence. Even to a greater extent than any of these, the recent advances in surgery have tended to give precedence in gynecologic residency training programs to modern techniques of radical pelvic operations almost to the exclusion of other aspects of gynecologic care.

It seems to be high time, then, to take a second look, and to ask ourselves if we are doing the job that is called for in what is undoubtedly the healthiest great nation in the world.

We have few nationwide statistics on the incidence of women's diseases, except for malignancy, but perhaps a more revealing index of the gynecologic

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health of America is provided by the sordid tally of sexual unhappiness and failures, of broken homes, illegitimacy and sterility, and of persisting maternal and infant mortality rates. It is said that some ten million Americans alive today have been involved in divorces. In one county in the Midwest, over a five-year period with 33,888 marriage licences issued, there were 22,748 divorce suits filed, and a half of these granted.[1] In 1950, there were 142,000 children born out of wedlock,[2] and estimates of over 300,000 criminal abortions annually have been considered conservative. The numbers of sexual delinquents and deviates are unknown. There are probably over 10 million married couples who have failed to achieve parenthood. I do not intend to present or discuss present-day obstetrical records tonight. It would indeed be inappropriate for me to do so, since to my regret, in my basic surgical training, I had no post-graduate obstetrics. I must therefore confine myself wholly to nonobstetrical gynecology—if indeed this is not an unacceptable paradox, since it can be reasoned that all sickness peculiar to women ties in directly or indirectly with the reproductive function. However, the figures quoted above speak eloquently of a degree of mental or physical sexual inadequacy, of maladjustment and parental immaturity, and give us a shocking picture of a state of ill health of the women of our Union.

If the medical profession is to accept the challenge of this grave problem, then the specialties of obstetrics and gynecology are primarily concerned. This is recognized in most teaching centers today. Just as modern obstetrics ranges far afield from delivery-room techniques, to include all phases of prenatal and postnatal care, so also present-day gynecology cannot be confined to pelvic operations or reconstructive vaginal procedures. The problem of the proper training of the gynecologist of tomorrow is that of emphasizing as well those disciplines that take into account the major elements leading a woman to seek advice for womanly complaints.

Considerably more than half of those who come into the gynecologist's office present difficulties that are nonsurgical in nature. In the clinical evaluation of these, it is just as necessary to recognize the emotional implications of the visit and examination, let alone of the complaint itself, as it is to know how to deal with anatomic relations and organic lesions of the female pelvis. Further, an awareness of the interplay of pituitary, adrenal, or ovarian hormones in pelvic disease may be of equal importance in many cases. To understand and to treat the complaints peculiar to the female sex, the gynecologist must have found the opportunity to grasp these interrelated disciplines, pelvic surgery, psychiatry, and endocrinology. Without some knowledge of these three essentials and of their interplay, one on another, this specialty will fail in what should be its primary goal—the comprehensive care of womankind.

Examples of the role of the emotions in endocrine dysfunctions are common in gynecologic practice. A 22-year-old unmarried girl recently sought advice for a two months' story of amenorrhea, an occurrence which had never happened before, but followed upon the first sexual exposure. When told that the pregnancy test had come out negative, she promptly had a period. A 29-year-old wife came to our clinic because of irregular periods and childlessness

after nine years of marriage. While undergoing endocrine assays, she missed two periods and the Aschheim-Zondek test was recorded as positive. She was referred to her obstetrician, but two months later returned, and her doctor's finding that the uterus had not enlarged was confirmed. It took two subsequent negative pregnancy tests to convince her that the desired conception had never occurred, and not until then did the abdominal distention, the engorgement of the breasts, and nausea recede, followed by a normal uterine flow. In this case of pseudocyesis, the wish for gestation produced not only the subjective symptoms, but also some hormonal factor that caused a recognizable congestion of the breasts and a false pregnancy test.

Such cases present two absorbing problems: First, they challenge the perspicacity of the doctor to make the correct diagnosis, and, second, they emphasize the unsolved puzzle of dysfunction of the reproductive system apparently due to the influence of emotions on endocrine secretions. These cases can be reduplicated in any clinic.

The importance of psychiatric and endocrine factors in almost every case demanding gynecologic surgery is not often as clearly recognized. Every operator, however, is familiar with the fact that two patients with identical complaints and undergoing similar operative procedures may recover entirely differently. One may have a rapid and secure convalescence while the other, without discernible physical complications, may yet be extremely slow, need much attention, more hospitalization, and even weeks after discharge seem incapable of assuming the usual social and household duties. An assumption is readily made in gynecologic practice that the emotional habitus of these patients, and the meaning of the operation to them may be deciding factors differentiating one from the other. It is never enough to remove reproductive organs and send a patient home with a healed wound without taking into account the effect of the hospital experience on marital, economic, and endocrine aspects of her home environment.

Surgery, psychiatry, and endocrinology—all three contribute to the complex pattern of management in gynecologic practice, varying from individual to individual, and the correct plan of treatment tests the skill and experience of the physician. The proper evaluation of the primacy of each of these disciplines is not always possible at the first visit; in many instances it is much easier to discern the most important feature only after the case is closed. For some complaints surgery is mandatory, yet endocrine and psychiatric support may play important adjunctive roles. In others, the maladjustment of the woman to life stresses may allocate precedence to psychotherapy over an elective surgical procedure. Finally, the major dysfunction may be endocrine, although a surgical experience may be necessary for diagnosis and psychiatric care for rehabilitation. It may be appropriate now, for emphasis, to present a few case abstracts as examples of these three categories of patients.

The first group includes two cases presenting gynecologic complaints primarily due to surgical pathology. We have been fortunate in the last three

years to have a team of workers assigned to our service consisting of three part-time psychiatrists, a psychologist, and a psychiatric social worker. Much of my material I owe to these associates.

CASE 1.—Mrs. M. C., a 38-year-old, divorced, para i, housewife was admitted for Stage I carcinoma of the cervix. She was an apparently jolly, affable, and obese woman who weighed something over 220 pounds, and her appearance belied the fact that three years previously she had been treated for a peptic ulcer. She later admitted that she had always been the strong, buoyant, helpful, and nursing member of her family, in which there had been numerous chronic severe illnesses, such as polio and diabetes in her father; a sister with rheumatic heart difficulty, a stepfather who died from leukemia, and her only child with colitis and vomiting as an infant. She was generally able to keep up a smiling front, but hemorrhage from her duodenal ulcer coincided with the stepfather's death and the sister's third and successful valvulotomy. Her prevailing concern has always been to keep up a strong front, and make trouble for nobody.

Five years before, she had had her first incident of menorrhagia treated with stilbestrol by a local doctor which satisfactorily stopped the flow after two months. Six months before admission, she again had similar uterine bleeding which she treated herself by taking one stilbestrol tablet daily without consulting her doctor. The bleeding would slow down after three weeks of this medication, so then she would stop. After a few days or a week the bleeding would start again, and she would take more stilbestrol. Her mother was aware of the bleeding and, three months before admission, had urged her to go to a doctor about it, but the patient's reply was, "I suppose I have cancer, and there is nothing to do about it anway." One week before admission, for the first time in her life, she struck her 13-year-old son for some rather minor reason, realizing later how much this boy, who had been born by a difficult breech delivery just before the divorce, was beginning to look like his father. The same day she was visited by her sister who learned about her bleeding and the patient was persuaded to come to the hospital and face up to the possibility of what she believed to be cancer. On admission she was found to have a large fungating growth, but limited entirely to the cervix. A radical hysterectomy with retroperitoneal pelvic lymph node dissection was done. She recovered rapidly from anesthesia without complaints, cooperating well with doctors and nurses. She had a few days of mild depression that she had predicted herself preoperatively, reminiscent of a rather major depression that followed her divorce 12 years ago. She has been encouraged by a good prognosis given on the basis that all of the lymph nodes had been negative, and the specimen showed no extension of the original growth beyond the cervix.

Comment.—The failure of this intelligent woman to seek advice through six months of bleeding may have been due to the fact that she had built herself up as the strong figure in the family, one who helped others in their weakness, and who had always smiled on the outside to prevent people from getting onto the fact that she was in a turmoil on the inside. This is her explanation for having developed a duodenal ulcer. She was unwilling to break this smiling façade, until inadvertently the break-through came in slapping her son. When finally she faced the fact that she had cancer, she summoned the defenses that she had used in previous crises to meet the fact, and has come through the operation with little difficulty. It may be of some interest that she took 1 mg. of stilbestrol off and on for six months without her doctor's advice at the time of her bleeding before entry, and to wonder whether this medication may not have had some connection with the fact that she had an exfoliative, large growth involving almost all of the cervix, which yet had not extended into any lymphatics or venous channels.

CASE 2.—Mrs. A. was a 26-year-old married woman who entered the hospital ten months after her fourth and last delivery because of prolonged and uncontrolled uterine bleeding. There had been three admissions at another hospital for curettage which had yielded no pathological cause. On admission to this hospital all studies of the endocrine system were

normal. There was no evidence of any blood dyscrasia; the uterus was not enlarged and because of obesity the ovaries were not palpable. She showed a moderate blood-loss anemia, and was bleeding profusely on entry. The patient was given intravenous estrogen over a 36 hour period which lessened but did not stop the flow. It was decided to do another curettage, her fourth within a year, before an exploratory laparotomy, at which time it was explained to the patient that if no obvious cause for the persistent bleeding could be found, a hysterectomy would be done. Because of her age, 26, the possible psychological connotations of hysterectomy were considered sufficient to ask for psychiatric consultation. It was further felt possible that some psychiatric element might play a part in the persistent bleeding of this previously fertile woman who had shown no etiological endocrine pathology. It was thought that the fact that Mrs. A. had asked on admission to have the uterus removed might have some bearing in this matter. It was not, however, until many interviews postoperatively, that the psychiatrist was able to elicit facts that may have played a part in this case. At operation the endometrium was grossly normal, and the uterus on laparotomy seemed to be perfectly normal but the ovaries were large, smooth, tense, and polycystic. It was felt at that time that this represented an unsuspected atypical case of so-called Stein-Leventhal syndrome with polycystic ovaries and a thick capsule, but associated with bleeding rather than amenorrhea. A large wedge was then resected from each ovary and the uterus was left intact. She had a relatively smooth convalescence and for 14 months after the operation her periods were normal, regular, at monthly intervals, and urinary pregnanediol determinations showed that ovulation had occurred with no recurrence of bleeding. In the postoperative course, the patient gradually came to describe some of the emotions attendant on her expecting to have the uterus out when she was admitted. She had three living children, but the fourth pregnancy resulted in birth of an anencephalic child, dead at birth. She blamed most of her immediate problems on this last episode. When she was shown the deformed infant she felt that the doctors had crushed the head by using forceps and were unwilling to admit it, and she became bitter and resentful and hostile to doctors since that time. It became apparent that, although she consciously wanted this child, there was considerable evidence that in her unconsciousness that she hoped that the child wouldn't live and was projecting this wish onto the doctors in order to mask her own guilt when the child was born dead. When she learned after the operation that she still had her uterus intact and could still become pregnant, she was at first resentful and unwilling to tolerate any discussion of possible ways to prevent pregnancy. Through frequent interviews with the psychiatrist in her follow-up course, she finally became more objective concerning her present situation and better able to accept the responsibilities of her motherhood. She is now pregnant again and happy in anticipation of her fifth child.

Comment.—It was felt that the tragic loss of the fourth child precipitated a conflict between her wish to stay immature without the responsibilities of further children and the necessity to meet the crises of her life. It is impossible to explain the unusual finding of polycystic ovaries together with the stigmas of obesity and hirsutism but associated with prolonged and persistent bleeding in a woman following her fourth pregnancy. It is difficult to escape the association of this ovarian pathology with the fact that, upon wedge resection, normal, regular and ovulatory periods followed without any further hormonal treatment. The surgical judgment shown in the resection of ovaries at time of laparotomy rather than removing the uterus must be evaluated in the light of the recognized emotional instability of this patient and the possibility that hysterectomy in a 26-year-old mother of three might have had far more devastating emotional complications than the return of this woman's reproductive system to normal function.

The next two cases represent women with gynecologic complaints that were best resolved by psychotherapeutic methods rather than by endocrine or surgical procedures.

CASE 3.—Mrs. E. J. A., aged 26 years, mother of two children, has worried about her scanty breast development since adolescence, considering herself unattractive compared with her mother. She had resorted to wearing "falsies" which, however, did not diminish her concern. This concern had recently reached a peak in an argument with her husband which made her fear that she might lose him for some other woman more attractive and buxom than she. At this time, she read an article in a popular magazine describing in glowing terms the achievements of plastic surgery in correcting undeveloped breasts. She took this to a local plastic surgeon who referred her instead to our clinic for possible endocrine treatment. It was agreed that an estrogenic ointment containing 0.5 mg. of stilbestrol per gram would be provided to be rubbed in twice daily for several months. It was explained to her that a certain amount of response could be expected, but that this would be only temporary and only as long as the directions were faithfully followed. This was fully understood and accepted. The only provision demanded was that she be willing to start and continue with psychiatric therapy to get at the underlying cause for her concern. In the psychiatric interviews that continued for six months, it soon became apparent that the concern over her breasts was only to cover up a deep feeling of inadequacy as a woman. She was much more concerned about sexual frigidity and an intense fury against her mother than about the problem that superficially presented itself as a lack of breast development. During the interviews, it was possible to work out some of the deeper reasons for her being inadequate. She had been brought up strictly by a critical and short-tempered mother who taught her that all sex was bad and dirty. She grew up aware of a strong hatred toward her mother, controlled only out of fear and guilt which made her feel that she was being bad and wicked. At the age of 18 she fell in love with a boy, and yielding to him became pregnant. When she told him about her condition, which was kept secret from her parents, he married her. She vividly recalls feeling worthless and being as much of a fake as her "falsies" when she walked down the aisle already pregnant. She could not rid herself of the feeling that her husband married her because he had to rather than because he loved her and, although she loved him, she felt unworthy, undesirable, and lived in the constant threat of impending disaster when her husband would discover how bad she was. In spite of the fact that she was married, sex relations always brought to her the feeling that she was doing something that her mother disapproved of, and from this came not only frigidity, but an accumulated hatred of her mother. She faithfully followed use of the ointment, and did get a small amount of response to the treatment; however, after the first three months of treatment, she began to get insight into the motivations of her difficulty and stopped using the ointment soon thereafter. A strong positive relationship was built with the therapist, and at the end of six months she was able to accept herself as a woman, improve her relationship with her husband and children, and experience satisfaction in marriage relations. She became again pregnant three months after ending her therapy, and was delivered of a normal infant, stating in her letter, "Our new member is a constant source of delight to us both."

Comment.—It was obvious to the gynecologist that stimulation of breast development with estrogen was not going to give a permanent answer to this patient's difficulties. When she became convinced that surgery was out of the question, then the hormone ointment was offered only to get her to cooperate in psychotherapy. In the course of a few months, this resulted in a highly satisfactory reorientation of this young woman, her attitude toward herself and her husband, and has resulted in what may be hoped to be a stable and firm and happy family union.

CASE 4.—Mrs. W. J. The next case involves dysmenorrhea. It is that of a student nurse who had cramps severe enough to lose at least one day every month from her training program. Due to this loss and that from intercurrent infections, she had fallen almost a year behind her classmates and was so discouraged that she contemplated dropping out of nursing altogether. On physical examination she seemed to be a normal, well-developed girl. There was an urgent need for some means to restore her confidence and give her courage to continue her schoolwork. We have become convinced of two factors consistently present in essential dysmenorrhea—the occurrence of ovulation, and a deep-seated insecurity or maladjustment

related to sexual function. It follows that there are two valid approaches to the relief of pain. The first, the elimination of ovulation, is only a temporary expedient; the second, a readjustment of basic insecurities, may take many interviews to accomplish, but promises in the long run the possibility of a permanent development of maturity and acceptance of the significance and meaning of menstruation. With Mrs. W. J., a knowledge of the proper dosage and timing of estrogen gave us the chance immediately to give her confidence that we could do something to prevent—not merely to lessen, but to eliminate her cramps and the time wastage they caused. A dosage system of oral stilbestrol was established so that she got through her last year having had but the three planned periods of pain at intervals on omission of the drug. At the same time, she began to see our psychiatrist and, over the course of a year, she found the sympathy and comfort of a parent-substitute. She was the oldest of three girls, but with two elder brothers. Her mother relied heavily on her for housework, and the younger sisters were never helpful, while the boys, because they were boys, went scot-free. W. J. was, indeed, extremely capable and accepted this responsibility in a grown-up fashion, except during menstruation. Then she became a very little girl, was completely helpless, demanded constant attention and had to be put to bed, petted, and fed. She grew to hate her mother and each month tried to prove that she, W. J., had far worse pains than those her mother was continually recalling from her youth. These and many other facets of adolescence were brought out, and finally understood and accepted in the interviews. When she graduated, we had agreed that she would discontinue hormonal treatment as a routine, since the pressure of graduating would be relieved. W. J. got along quite well with mild sedatives during the next six months. A "boy-friend" problem was resolved by marriage, and she became pregnant soon after. She came in once to see us with her young son; cramps were a thing of the past, she had become a mature woman.

Comment.—The disabling cramps in this otherwise healthy girl threatened her career. Many types of sedatives had been tried without preventing loss of time from school. She was facing the real possibility of resigning as a failure. The complete elimination of dysmenorrhea on suppression of ovulation confirmed our impression from a negative pelvic examination that the pain was functional, not organic. A presacral neurectomy, except for the time lost due to the operation, might have given her relief but, we felt, would not affect in any way the deeper reasons for her abnormally severe reaction to menses. The use of estrogen provided relief for the time necessary to surmount her basic insecurities by psychotherapy.

In the last category of case reports, I want to include two in which the presenting gynecologic complaint was found to be caused by some primary endocrine abnormality with psychiatric or surgical implications.

CASE 5.—Miss A. S. was first seen at the age of 25 years when a postgraduate student at a near-by college. The menarche occurred at 12½ years with regular periods for five years and then she first skipped 2 months which she believed due to bathing in cold water. She had one more menstrual flow following the use of Lydia Pinkham's extract, but no other spontaneous flows since that time. She had had many colds, occasional headaches, and had been found to be anemic on occasion. One year previously, she had been given hormone shots without response. Her history was otherwise negative. Examination showed a thin girl with nails bitten down to the quick; with fine blonde hair, normal pubic escutcheon, a feminine build, undeveloped breasts, and normal genitals. The mass of the uterus was infantile and nothing could be palpated in the vaults. Further history disclosed that the summer of her amenorrhea she left the protective influence of home in a small town to go to a large western university where a great deal was made of social life, sororities, and so on. She failed to make any of the sororities, rating herself as an "independent" which was a synonym for "outcast." She therefore applied herself to her studies, made Phi Beta Kappa, concentrating on chemistry, psychology, and German. She transferred to another university for an M.A. degree because of her unhappiness in college, but did not make the grade, and after

a year gave it up and went to Germany to study as a postgraduate student for a year, where she lived with a German family whom she found diffident, cold, and difficult to get along with, and after another unhappy year came back to work for her Ph.D. At this time, she felt convinced that her difficulty was psychological, and thus her fault, and therefore she had not previously consulted a doctor. The gynecologist tentatively agreed with this self-diagnosis but planned an assay of routine endocrine indices as well as an x-ray of the pituitary gland while instituting psychotherapy. The x-ray showed "ballooning of the sella to 20 mm. by 14 mm. with thinning of the posterior clinoids, consistent with chromophobe adenoma of the pituitary." The tentative diagnosis of hypothalamic or emotional amenorrhea had seemed justified by the story given by this patient. This is never sufficient grounds for failing to perform the usual diagnostic tests, however. The patient was given radiation treatment, and the visual fields will be carefully followed. If any progressive encroachment on sight is noted, then surgical extirpation of the tumor will be done.

CASE 6.—Miss C. I. is a 28-year-old girl who came to the clinic complaining of secondary amenorrhea. Her history was that of normal development with menarche at 12 years, regular for the first 3 years, but after 15 becoming less and less regular and for the last 10 years there had been no periods at all. The patient was extremely well educated, well oriented, and quite feminine, and had carved for herself an important career in an executive capacity which she was fulfilling eminently satisfactorily. There was no history of acute illness. Physical examination showed a well-developed girl with no signs of masculinization, no hirsutism, and no obesity. Endocrine study showed a normal pituitary fossa, normal FSH assay in the urine, normal values of adrenal corticoids. The vaginal smear showed a slight estrogen deficit but not a wholly atrophic smear. Pelvic examination showed the uterus to be small in size, the ovaries nonpalpable. With the story of secondary amenorrhea in the absence of any signs of virilizing tumor, yet with a nonelevated FSH determination, it was felt that this might represent a case of emotional or hypothalamic block of pituitary hormone release. The patient was referred to a psychiatrist.

In repeated interviews, it was revealed that this patient was struggling with a conflict between wanting to continue in her career in competition with the men of her acquaintance and her normal desire to be a female. She had from time to time attracted many men but had always refused to get involved because of the innate conflict in her life as to whether or not she would rather have been a man or a woman. It is interesting that twice during the psychiatric interviews she came to a decision toward femininity and each time the urinary pregnanediol excretion showed positive tests although no periods resulted. At this point it became important in her psychotherapy to gain some definite answer as to whether or not there was any organic lesion in the pelvis which prevented further periods. The patient agreed to an exploratory laparotomy. The uterus was found to be immature and infantile in type and in each vault was found a small linear fragment of whitish tissue that was the only evidence of any ovarian remnant. This was almost the same picture as that seen in cases of ovarian agenesis. Biopsies were taken which showed no ovarian follicles or ova whatsoever in either ovarian fragment. It was concluded that in this case the gonads were genetically deficient, having only sufficient follicles and eggs to respond for the first few years after menarche, during which time the female contours and habitus were developed. The patient was told of the evidence that there was apparently no possibility of her having normal periods or children of her own. She was able to master this tragic news with the help of the psychiatrist and has started to build her life anew with this knowledge in mind.

Comment.—This case taxed the ingenuity of the diagnostic endocrinologist to find the cause for secondary amenorrhea in a girl who showed tremendous conflict between her desire and competence in a masculine role and her innate femininity. She might have continued for a period of years under various endocrine treatments or else under the care of the psychiatrist alone and it is quite possible that in either case the organic basis for her complaint might never have been suspected. The surgical demonstration of almost completely agenetic ovaries

gave the answer. The normal FSH levels are difficult to explain except on the basis that adrenal estrogen production must have compensated for the failure of the ovaries in this otherwise normal young woman.

In summary, these few cases have been presented as examples of women with complaints that brought them primarily to a gynecologist, yet their problems involved psychiatric and endocrine factors in varying degree. Such cases are in no way unique; similar stories are encountered daily by those in this audience. There are almost inevitably to be found emotional and often endocrine aspects of significant importance in women facing surgery as well as those with functional complaints.

Fifty years ago the foundations of modern psychiatry and endocrinology were being developed and these disciplines then rapidly became so specialized that it was difficult for most surgeons to encompass even their basic principles in a training program. At the same time, the specialty of gynecology was making tremendous strides in operative technique. Inevitably in some centers the emphasis on surgery detracted from teaching an awareness of the complex background implicit in the nature of the female. Yet a careful evaluation of the various factors involved in each woman's difficulty, as emphasized in these case reports, brings out the inadequacy of dealing with only one aspect of the individual problem. If gynecologists are to treat adequately the difficulties peculiar to women, they have readily available today the tools of psychiatry and endocrinology to make such treatment comprehensive.

The nation's health is measured not only by mortality statistics, but also by the strength of the functional unit of our civilization—the family and its stability. To an overwhelming degree, the controlling element in this unit is the attitude and sexual maturity of the wife and mother. We cannot feel proud of the current reckoning in terms of divorces, abortions, illegitimacy. The specialities of obstetrics and gynecology must take considerable responsibility for improving this record, for they are committed to dealing with those intimate aspects of the life of our women touching the reproductive sphere. We can no longer afford to regard our obligations to our residents fulfilled when we have taught the technique of tumor extirpation. We must recognize the need for a wider perspective in the training of those in whose hands the gynecologic health of the nation will rest. We must see our way to include in our residency programs the essentials in psychiatry and endocrinology related particularly to the problems of women, and then teach the need for integrating all available facts into the completed picture of the individual woman with a complaint. It may be pertinent to recall the old story of the father who was attempting to read the Sunday paper while his small son continually struggled for attention with childhood's always reliable excuse, "What can I do now, Pa?" After the tenth suggestion, the harrassed father finally found a map of America in the paper and with the scissors cut it up into a number of pieces. Giving it to the boy as a picture puzzle, he then settled back, confident of at least some minutes of peace. A moment later, however, the

son was back again with the puzzle completed. "How did you do it so fast?" "Oh," said the boy, "I found a picture of a lady on the other side, so I put the lady together and the country took care of itself!"

We must then somehow plan to give our young men the technical proficiency of present-day obstetricians and surgeons, the perspicacity of the endocrinologist, and something of the wisdom of the psychiatrist, in order to provide specialists equipped to give adequate care in comprehensive gynecology. Let us hope that, thus equipped, they can, like the small boy, pick up the pieces and put together again the women who come for their help, and then our country may be better able to take care of itself.

I wish to acknowledge with grateful thanks permission to use pertinent material in the case reports from my associates, Drs. Doris Menzer, Phillip Gates, Thomas Morris, and Joseph Sabbath, psychiatrists, and Mr. Thomas Plaut, psychologist.

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Case Reports, New Instruments and Methods

A FETAL HEART RATEMETER*

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EVER since Höber[1] in 1919 first demonstrated the adult heart sounds by means of a radiocircuit, there has been interest in applying this technique to auscultation of the fetal heart. Keiper[2] reported that Abbott used a telephone transmitter and loudspeaker as early as 1922 to demonstrate the fetal heart in a large room. Additional reports of success in amplifying the fetal heart sounds appeared in 1923 from Beruti[3] in Argentina, Schäffer[4] in Germany, and Falls and Rockwood[5] in the United States. Since 1923 there have been some seventy publications dealing with amplification and recording of the fetal heart.

The advantages of continuous observation of the fetal heart sounds during labor, from both the clinical and the research standpoint, are obvious. Unfortunately, as attested by the many publications referred to, it is difficult to amplify and record the fetal heart sounds. No listening apparatus yet designed has the same ability as the human ear and brain to discriminate satisfactorily between a number of sounds of similar frequencies such as those produced by maternal and fetal movements, maternal circulation and digestive noises, friction between the microphone and skin, blankets, or clothing, and by happenings in the vicinity of the patient. Furthermore, noise in the amplifying system and acoustical feedback between the microphone and loudspeaker are troublesome.

These difficulties can be more or less satisfactorily met, but the resulting instruments are cumbersome, expensive, and often uncertain in performance. Hence, they are scarcely suited to regular clinical use. Some interesting information has been obtained, however, from relatively short periods of observation of the fetal heart sounds during pregnancy and labor. In addition to measurements of the intensity and duration of the first and second sounds and of systole and diastole,[6-17] studies have been made of the differences between the hearts of twins,[18-19] of congenital heart defects,[20-23] of the transformation of fetal heart sounds to neonatal heart sounds,[16, 17, 24] and of the variations in heart rate under normal conditions, and as influenced by anoxia, gases inhaled by the mother, drugs, and pressure on the fetal head.[8, 11, 16, 25-36]

*The development of this instrument was made possible by a grant from United Cerebral Palsy Associations, Inc.

It is obvious from past obstetrical experience and from a study of the literature that careful observation of the fetal heart rate is the most reliable index of the condition of the fetus we have. The studies of the fetal heart rate alluded to above, however, have not revealed anything that is not already known from auscultation with the human ear. The one advantage of these previous electronic recorders of the fetal heart rate is the elimination of human error in counting the rate. However, the mechanical difficulties in providing long periods of observation, together with the problem of counting from the records the rate of a phenomenon occurring 140 times a minute on the average, have limited electronic recording of the fetal heart to the better documentation of long-established clinical observations. Only an instrument that will respond chiefly to sounds with a more or less regular rhythm and that is capable of counting the rate of these sounds can offer us better information. Such a device, to be completely successful, must also be relatively simple, not too expensive, and rather reliable.

The difficulties inherent in fetal heart rate metering from the heart sounds are such that one might consider some other approach to counting the heart rate. Devices using the R wave of the electrocardiogram to trigger a ratemeter circuit have been developed for the adult heart rate.[37, 38] The extensive literature demonstrating that the fetal electrocardiogram can be recorded has been thoroughly reviewed recently.[39] Only a few investigators, however, have been able to demonstrate deflections from the fetal heart in every case. Furthermore, the method is not satisfactory for heart rate metering because of interference from maternal cardiac and uterine muscle action potentials, and because of the uncertain but usually minute amplitude of the fetal R wave. One author[40] also attempted to record the ballistic reaction of the fetal heart, but was unsuccessful because of interference from the maternal heart and maternal movements.

Our instrument represents an effort to make possible an instantaneous count and record of the fetal heart rate utilizing the heart sounds. In our hands in preliminary testing it has proved to be relatively simple to operate, and relatively reliable. It is to be hoped that it will provide considerably more information than has hitherto been available from both the research and the clinical standpoint. Although our investigations are only in their preliminary stages, we are publishing the details of the fetal heart ratemeter in the belief they may be helpful to other investigators.

The Fetal Heart Ratemeter

The fetal heart ratemeter consists of a contact type crystal microphone, an amplifier equipped with a loudspeaker for monitoring the heart sounds, a multi-vibrator type ratemeter, and a suitable power supply. The fetal heart rate may be read from a meter or can be recorded for later analysis.

Microphone.—Experience with various types of microphones led us to choose the Brush D. P. 1 H crystal contact microphone. This microphone was designed to pick up adult heart sounds, but is sensitive enough to pick up most near-term fetal hearts. We have not found it satisfactory when the heartbeat is faint as in early pregnancy and in extremely obese patients. Furthermore,

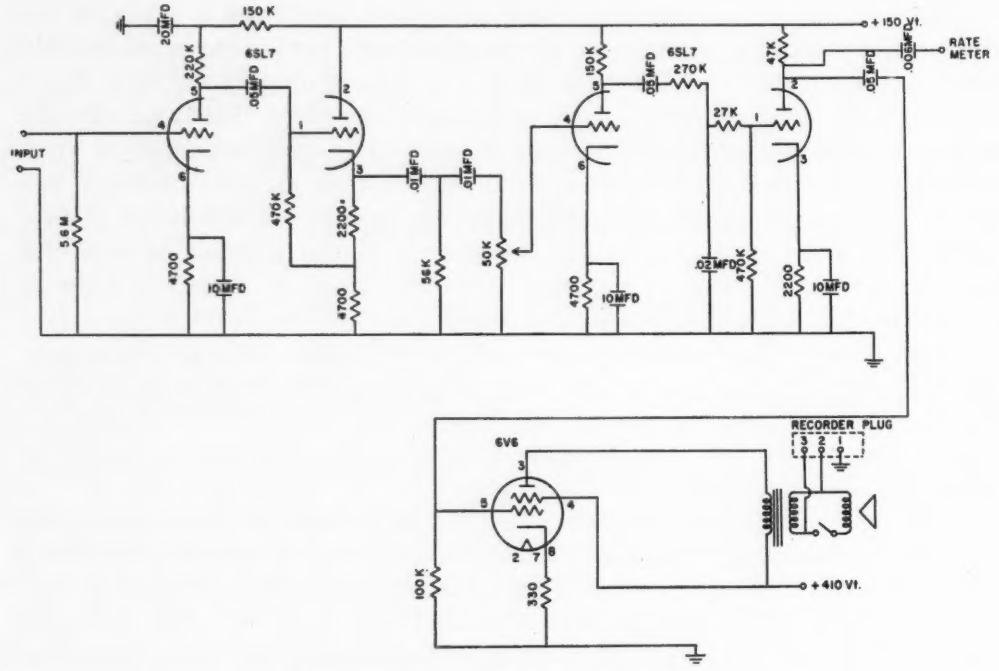


Fig. 1.—Circuit diagram of amplifier.

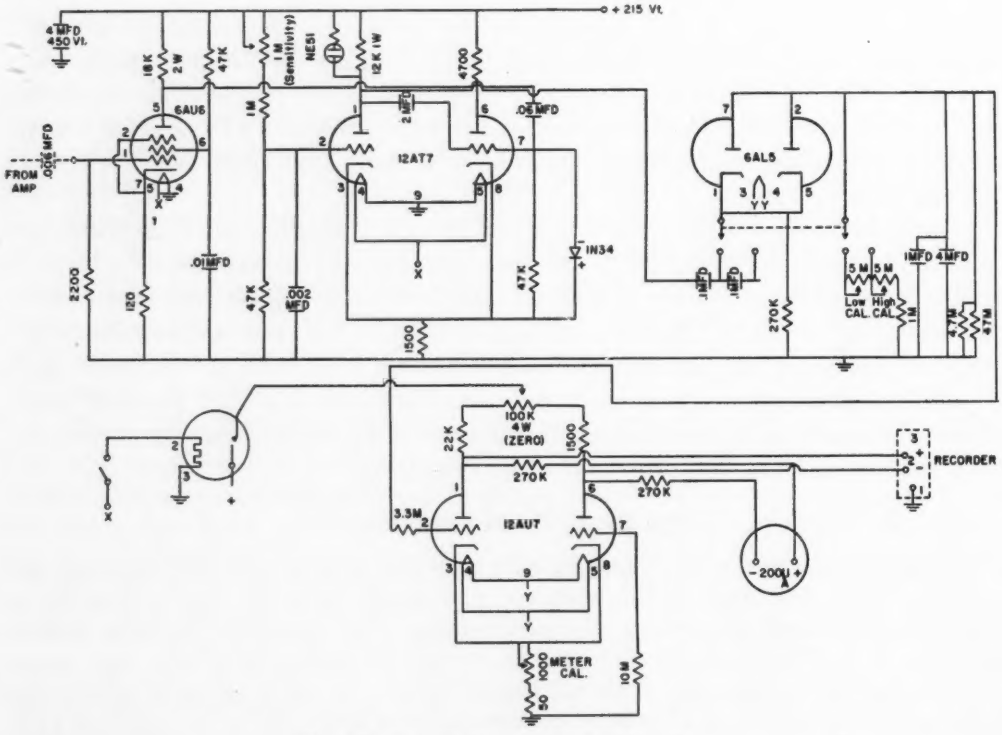


Fig. 2.—Circuit diagram of ratemeter.

it must be placed over the point of maximum loudness of the heartbeat in order to be effective. These disadvantages, however, are outweighed by the virtual elimination of interference from external noises and adventitious sounds from within the abdomen, which are quite troublesome when other types of microphones are used.

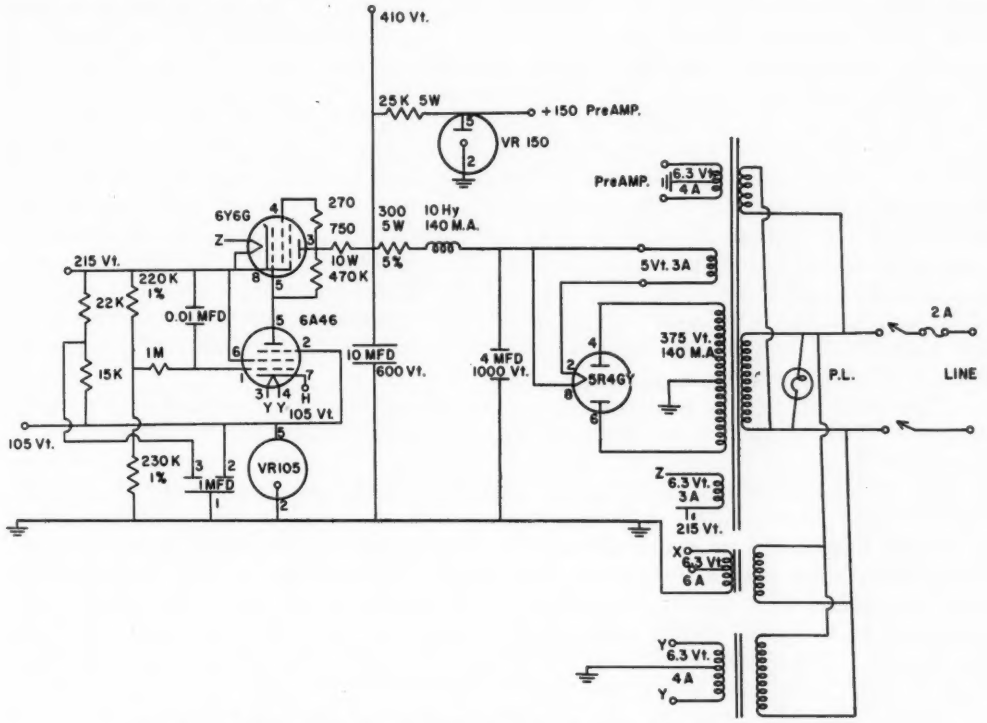


Fig. 3.—Circuit diagram of power supply for amplifier and ratemeter.

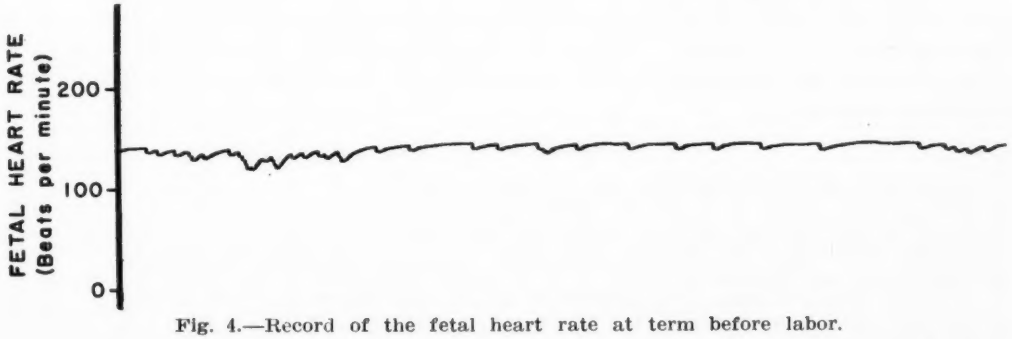


Fig. 4.—Record of the fetal heart rate at term before labor.

It is necessary to have a mounting for the microphone of sufficient weight to provide considerable pressure against the abdominal wall and to hold the microphone perpendicular to the abdomen. We have mounted the microphone on a ¼ inch brass plate threaded into a 3 inch long collar of brass tubing 3 inches in diameter and ¼ inch in thickness. The pressure of the microphone against the abdomen can be varied by screwing the plate up or down within the tube. This mounting will maintain its position well when lightly strapped to the patient with one or two 1 inch straps.

Amplifier (Fig. 1).—We have found the amplifier described by Steer and Hertsch[41] to be satisfactory, with only slight modifications, for amplifying the signal from the microphone. The amplifier drives a small speaker for auditory monitoring of the fetal heart.

Ratemeter (Fig. 2).—The signal from the amplifier is further amplified and shaped, and then fed to a one-shot multivibrator. In order not to count both heart sounds, should they be present, the multivibrator was designed to have 0.2 second time constant. Thus, any signal occurring within 0.2 seconds of another will not trigger the multivibrator and will not be counted. Since the two sounds of the relatively slow adult heart are less than 0.2 seconds apart only the first sound will be counted, and the normal adult heart may be used to calibrate the instrument. This long time constant also serves to eliminate some background noise and hum from the amplifier. Furthermore, the sensitivity control is adjusted so that only the relatively large signal from the heartbeat will trigger the multivibrator. Since the output of the multivibrator is constant regardless of the intensity of the input signal (provided the signal is large enough to trigger the multivibrator), this output is proportional to the number of triggering signals and independent (within limits) of the intensity of the signals.

The output of the multivibrator is rectified and charges a low loss condenser. This condenser is shunted by a variable resistance to form an R/C circuit with a time constant of about 15 seconds. The charge on the condenser is now proportional to the average number of signals triggering the multivibrator per 15 seconds. A longer time constant could be used, but in order to detect any rapid or short changes in heart rate the shortest time constant compatible with stable operation was used. The charge on the condenser is read by means of a balanced bridge vacuum tube voltmeter. By proper adjustment of the calibration controls the heart rate may be read directly from the meter. A neon lamp in the multivibrator plate circuit flashes with each beat to serve as an additional monitor of the fetal heart rate.

Power Supply (Fig. 3).—A suitable power supply is provided to power the amplifier and ratemeter circuits.

The recorder which we have employed to provide a written record of the fetal heart rate (Fig. 4) is a four-channel Sanborn, series 150 with a DC coupling amplifier in the input. This is a voltage recorder. If a circuit type recorder is used the voltmeter circuit would have to be redesigned to supply the necessary current.

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A RECORDING SPHYGMOMANOMETER*

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THERE are a number of occasions in clinical and research work when an automatic recording sphygmomanometer would be useful. A number of such instruments have been designed, but most of them have not been completely satisfactory.

The automatic recording sphygmomanometer recently developed by the National Bureau of Standards is the most successful yet designed.[1] The instrument is capable of measuring systolic and diastolic pressure consecutively with moderate accuracy and good repeatability, is direct indicating, comfortable to the patient, and safe for unattended operation. In addition, it has two features essential to its use during anesthesia (for which it was specifically designed). First, between cycles of measurement it displays on dials the latest blood pressure measurement. Second, it is insensitive to sounds other than those from arterial pulsations. These two features, while essential during anesthesia, add considerably to the complexity and expense of the instrument.

This report describes a somewhat simpler and less expensive modification of the Bureau of Standards instrument. Our modified version of the recording sphygmomanometer was designed for investigation of the maternal blood pressure during labor. Its major difference from the original apparatus, therefore, is in the elimination of the two features previously mentioned which were specifically designed for use during anesthesia for general surgery.

The Recording Sphygmomanometer

The instrument has two major components. The first is a system for automatic cyclic inflation and deflation of the blood pressure cuff and for recording the consequent changes in air pressure within the cuff. The second is a microphone and amplifier system for picking up the arterial pulsations and superimposing them on the recording of the pressure changes within the blood pressure cuff.

Pressure Recording System (Fig. 1).—Air pressure inflates the cuff under control of a timer. When the timer cycle closes the relay, the normally closed solenoid valve opens to admit pressure to the system and the normally open solenoid valve closes to permit the build-up of pressure within the system. The blood pressure cuff inflates over a period of about 90 seconds to a prechosen pressure cutoff point (usually 200 mm. of mercury). The pressure switch then opens and the solenoid valves return to their normal positions

*The development of this instrument was made possible by a grant from United Cerebral Palsy Associations, Inc.

deflating the cuff in a few seconds. The timer restarts this cycle every three minutes. A manual control switch is provided so that the inflation cycle may be started independently of the timer.

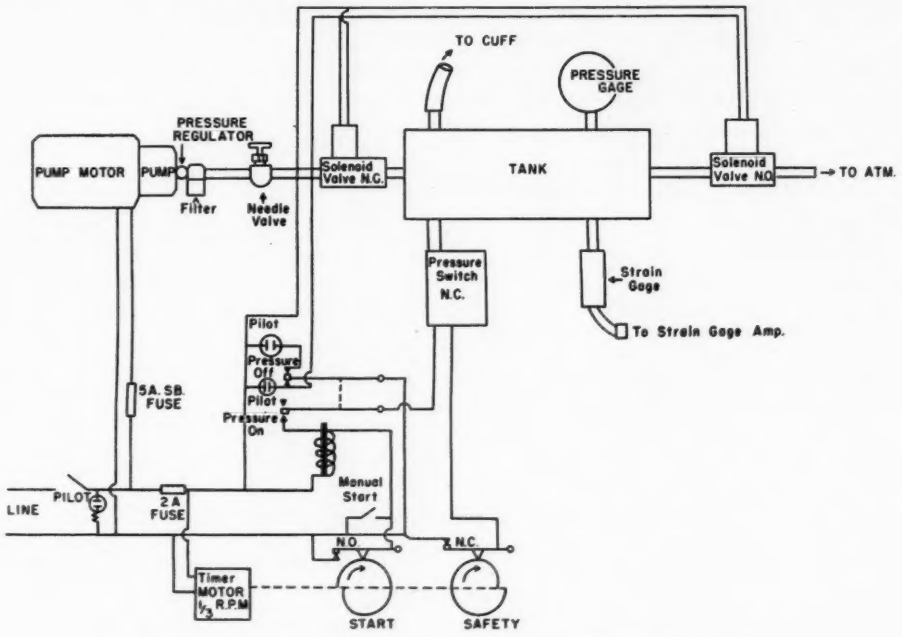


Fig. 1.—Circuit diagram of the pressure recording system.

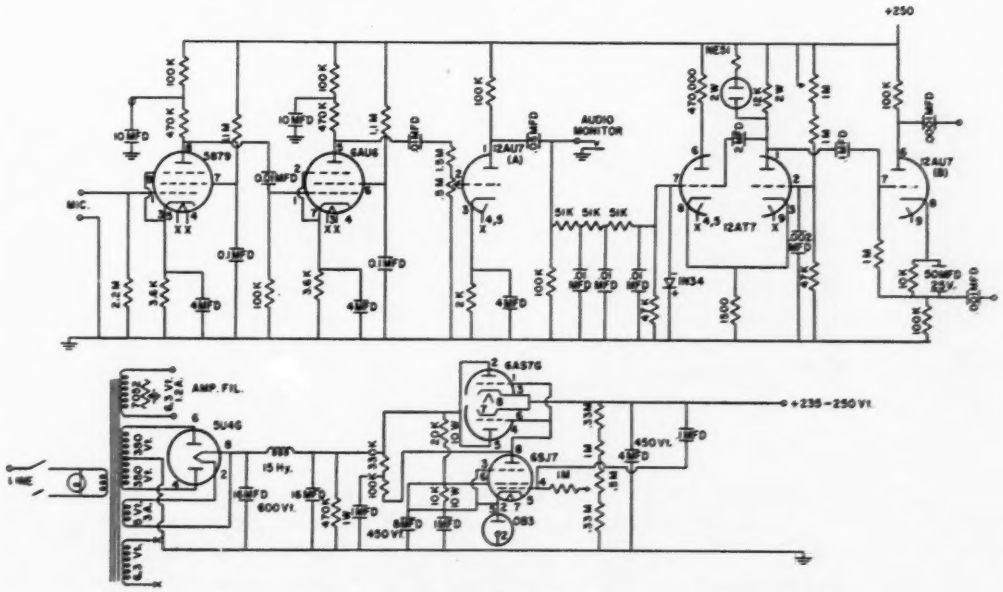


Fig. 2.—Circuit diagram of the amplifier of the sound recording system.

Safety of the patient is maintained in several ways. The pressure switch will, of course, open and deflate the cuff as soon as the pressure reaches the cutoff point. In the event of failure of the pressure switch to open, the timer

safety switch will automatically break the circuit after 90 seconds, thus deflating the cuff and preventing prolonged application of excessive pressure to the patient's arm. In the event of power failure the solenoid valves will return to normal position and deflate the cuff.

The pressure within the cuff is recorded with a strain gage. We are using a strain gage with a range of 0-5 pounds per square inch which is sufficient for measurement of even excessively high blood pressures. The output of the strain gage is amplified for recording on a Sanborn 150 series recorder by means of a carrier amplifier.

Sound Recording System (Fig. 2).—The crystal microphone for picking up arterial pulsations is mounted in a suitably shielded diaphragm-type stethoscope head similar to that employed in the Bureau of Standards instrument.

The amplifier is also adapted from that employed by the Bureau of Standards. A neon bulb is led off the multivibrator plate circuit. This bulb, accordingly, flashes each time a pulse triggers the multivibrator. Thus, it allows proper adjustment of the sound level from the microphone to that just sufficient to trigger the multivibrator. The output of the amplifier is fed into the output of the strain gage carrier amplifier so that the arterial pulsations appear as excursions from the pressure curve and thus indicate the actual blood pressure on the record (Fig. 3).

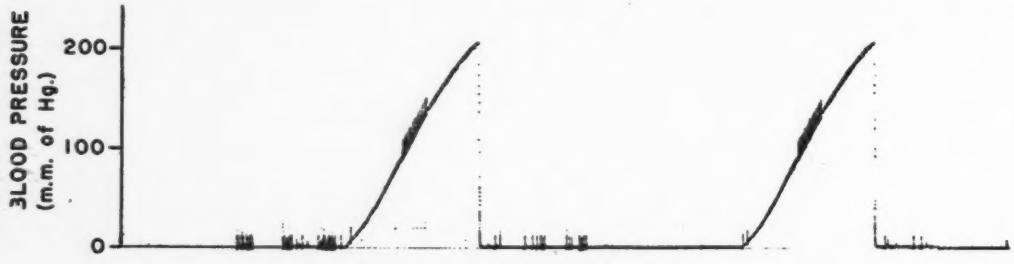


Fig. 3.—Recording of maternal blood pressure.

Use of the Instrument

The microphone is applied to the brachial artery above the antecubital space. It is held in place by a strap and a ring of double-faced Scotch tape. The Scotch tape eliminates friction noises from the skin and insulates the microphone somewhat from external noises. The blood pressure cuff is then applied over the microphone. This further decreases the pickup of noise by the microphone. Between measurement cycles some external noises and the movements of the patient's arm will cause deflections on the record (Fig. 3), but these sources of interference are effectively sealed off from the microphone as soon as the cuff begins to inflate.

After the attachment of the microphone and blood pressure cuff, the instrument is run through several cycles while the gain control of the amplifier is adjusted to the characteristic sound level of the patient. This is a fairly simple adjustment. The gain control is advanced until the neon bulb pulse indicator just begins to pulsate at the level of the predetermined auscultatory diastolic pressure of the patient. This level of gain is left undisturbed after the initial setting.

The instrument has been used on many different subjects for periods up to six hours without apparent discomfort to the patient. Trials of different

measurement cycles and varying lengths of cuff inflation time have demonstrated that cycle intervals under 3 minutes and inflation times over 2 minutes do create discomfort when measurements are continued over several hours. When the inflation time is less than 90 seconds, the record obtained is unsatisfactory for easy interpretation.

This apparatus, of course, reverses the usual manner of obtaining the blood pressure in that readings are taken during inflation of the cuff rather than during deflation. The points of initiation and disappearance of sound are quite sharp, however, and repeated comparison of the blood pressures obtained with this instrument and with the accepted auscultatory method have demonstrated good agreement in all blood pressure ranges. Often the two methods yield the same result. The maximum variation we have as yet found is 5 mm. of mercury.

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INTRAPARTUM RUPTURE OF BILATERAL OVARIAN ENDOMETRIAL CYSTS

Case Report

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(From Mount Sinai Hospital, Chicago)

THE following case report is presented because it entailed a difficult problem in diagnosis, and because it was a very interesting, unusual, and rare pathological picture.

B. R., a 38-year-old white woman, gravida iii, para ii, at term was admitted to the Mount Sinai Hospital birth rooms on April 28, 1955, at 3:10 A.M. Her previous obstetrical history included two spontaneous deliveries (1945 and 1949) which were uncomplicated.

The patient was seen by her doctor at home at 1 A.M. on April 28, 1955, because of sudden excruciating, diffuse abdominal pain. Examination revealed a tense abdomen, distended by a full-term pregnant uterus which felt hard and was tender on palpation. The fetal heart tones were 120 per minute.

In the hospital the pain and hardness of the uterus remained constant and the fetal heart tones were not heard. Oxygen by mask was given, along with 100 mg. Demerol. Shortly after this treatment, the uterus relaxed somewhat but the abdomen remained tense. The fetal heart tones were now heard at 124 per minute but were irregular and weak. There was no evidence of vaginal bleeding and a rectal examination showed that the cervix was thick, admitting only a finger tip. The blood pressure was 130/80, pulse 72.

The patient seemed very anxious and apprehensive. A tentative diagnosis of abruptio placentae with concealed hemorrhage was made and the patient was prepared for a cesarean section. The fetal heart tones became regular and moderately strong.

The erythrocyte count was 4.17 million, hemoglobin 12.1 Gm. per cent, leukocytes 13,000.

Under local anesthesia, the abdomen was opened and a large amount of chocolate-colored fluid poured out. A low cervical section was performed. The amniotic fluid was clear and delivery of a normal, viable male, who cried spontaneously, was accomplished. The uterine incision was closed in layers.

Both ovaries were found completely replaced by large cysts which had previously ruptured spontaneously. A total hysterectomy and bilateral salpingo-oophorectomy were performed. The patient received 500 c.c. of whole blood during the operation. She was placed on antibiotic therapy (Achromycin), made an uneventful recovery, and was discharged on the ninth postoperative day.

The pathological report revealed a right ovary almost completely replaced by a previously ruptured cyst measuring 15 cm. in diameter. The outer surface was smooth and glistening and the wall measured 5 mm. in thickness. The inner surface was covered with old clotted blood and had a dull appearance. The ovarian tissue from the left side measured 5 by 3 by 2 cm. and intimately attached to it was a previously ruptured cyst similar to the one described on the right side, measuring 7 cm. in circumference.

The pathological diagnosis was endometrial cysts with decidual reaction and focal ossification in the left ovary.

Summarizing, then, this is a case of endometriosis of both ovaries which had ruptured spontaneously when the fetal head had descended through the pelvis.

A search of the literature to date suggests that endometriosis in pregnancy is infrequent, and particularly bilateral spontaneous rupture of endometrial cysts by the fetal head in descent. This subject was first mentioned in standard textbooks by Eastman[1] in 1950.

Sampson[2] in 1922 reported the first case of pregnancy and ovarian endometriosis. From 1922 to 1944, seven more instances of this combination of conditions appeared in the literature. In 1944, Scott[3] described the one and only case of the rupture of an endometrial cyst as a complication of pregnancy in a 25-year-old primipara at 36 weeks' gestation. Scott's second patient was a 23-year-old primigravida with a large ovarian endometrioma at 12 weeks' gestation, unruptured.

Ware[4] in 1950 reported 13 cases of endometriosis in pregnancy; in 12 of these, pregnancy occurred after a conservative operation for endometriosis had been performed. The thirteenth patient had endometriosis during pregnancy but it was undiagnosed until she was delivered by cesarean section.

Gainey and associates[5] in 1952, added 38 instances of endometriosis in pregnancy, not all of which were confirmed by histopathological evidence. A decidual reaction of the endometrial stroma in these cases of endometriosis in pregnancy was almost a constant finding. It is important to note that a positive diagnosis histologically is often hard to make in pregnancy because this decidual reaction obscures the adenomatous elements so that they are found only with great difficulty. Gainey did not report any cases of ruptured endometrioma in the third trimester of pregnancy.

The literature suggests that endometriosis and pregnancy may coexist without untoward consequences unless rupture of these endometriomas occurs, as happened in the case presented.

This case then should stand as the second one reported in the literature wherein ovarian endometriomas were ruptured spontaneously by descent of the head and the true diagnosis was obscured because the symptoms simulated those of abruptio placentae.

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MONOAMNIOTIC TWINS WITH DOUBLE SURVIVAL

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DIETRICH[1] has been quoted as saying: "It is given to no obstetrician to see more than one case of monoamniotic twins in his experience." With this thought in mind it seems worth while to report such a case when seen rather than to wait to accumulate a "series." The incidence of this condition is rare. Quigley[1] in 1935 reported a total of 109 cases collected from the world literature with a survival of both twins in only 17 cases. Single cases have appeared from time to time since the original review and many of these cases have presented bizarre situations. Litt and Strauss[2] had a case of monoamniotic twins in which one showed normal development and the other was anencephalic. These twins were stillborn because of multiple true knots in the cords. Caldwell's[3] case was complicated by a brow presentation and eclampsia. His twins were delivered by cesarean section.

The first case of double survival in the American literature was that reported by Parks and Epstein[4] in 1940. These babies were one month premature and true knots were present in the cords.

In 1952 King and associates[5] reported 5 new cases, bringing the reported total up to 148 cases of monoamniotic twins with 38 double survivals and 25 single live births. Five of these latter had congenital defects of various types.

Hollaender[6] in 1953 found three cases occurring from 1900 to 1953, which, added to the latest American reports, bring the total number in the world literature up to 166, including the case herein reported. This additional case of double survival brings the current number to 40 cases in which both twins have survived. This is an incidence of 24 per cent.

The "primitive duality" theory[7] of twins occupying a single amniotic sac is based on the supposition that originally there are two amnions and that the partition between the two sacs is broken down early in fetal life. This is thought to occur between the seventh and thirteenth days. Pulsation of the closely approximated cords on each side of the partition is credited with being one cause of the breakdown between the two sacs.

The "primitive unity" theory maintains that during embryonic development the two blastodermic vesicles meet and join and are enveloped by one amnion.

Logically, all cases of monoamniotic twins are single ovum twins. Single ovum twins represent 36 per cent of all cases of twins, according to Corner.[8] It is with this group that we are chiefly concerned. In his report on the embryology of single ovum twins, Corner illustrates a very logical theory of the

formation of monoamniotic twins by their development on a single germ disc (Fig. 1, *C* and *D*). His report also illustrates a double monster in an intact amnion, the age of this specimen being 28 to 30 days' gestation. It provides absolute proof that twinning may occur after the amniotic cavity has formed.

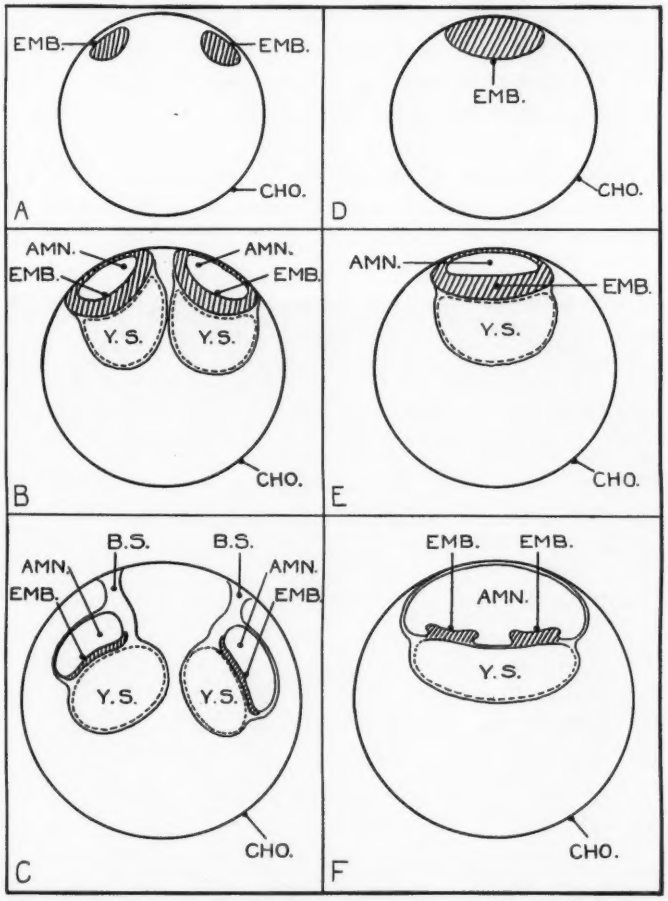


Fig. 1.—Diagrams illustrating two types of single-ovum twinning in man. *A-C*, By formation of two inner cell masses. *D-F*, By formation of two embryos on a single germ disc. (From Corner, G. W.: Bull. Johns Hopkins Hosp. 33: 389, 1923.)

The clinical importance of the monoamniotic twinning is the danger of death to one or both of the fetuses from twisting or knotting of the umbilical cords, which is very common. There is little or no increased risk to the mother in the monoamniotic state of her twins, but to the fetuses it is of very serious import in that the survival rate of both twins is so low. Cases have been reported where the cord of the second twin was around the neck of the first twin. The cord was cut in order to facilitate delivery. Only then was it found that the cord belonged to the unborn twin. Prompt delivery of this second twin is essential in order to save its life.

Case Report

Mrs. C. M., a 25-year-old white para i, gravida ii, was at term on Oct. 30, 1955. Her prenatal course was normal except for 1 plus sugar in the urine on four successive examinations. The last office examination prior to hospitalization was on August 29 at which time

she complained of some swelling of the feet. Twinning was suspected on this visit but two fetal heartbeats could not be heard and x-rays were deferred until the next appointment. On September 24, at 35 weeks' gestation, the patient went into labor after the spontaneous rupture of the membranes. After 1½ hours, dilatation was complete and a 4 pound, 12 ounce female infant was delivered spontaneously from left occipitoanterior position. There was no second amniotic sac and a breech extraction of the 3 pound, 1 ounce female was effected without difficulty. The cord of the second twin was half the size of the cord of the first twin and was entwined about the latter six or seven times. There were no true knots in either of the cords, which probably accounts for the survival of these twins. There was considerable constriction of the second baby's cord, however, which was undoubtedly the cause of the marked discrepancy in the size of the cord and the child. There was no remnant of amniotic membrane whatsoever between the two cords, the single amnion being continuous with the margin of the single placenta (Fig. 2).



Fig. 2.—Placenta of monoamniotic twins. Note the wide separation of the points of origin of the two umbilical cords.

Unfortunately, the cords were disentangled before the photograph of the placenta was taken, but it shows the considerable distance between the origin of the two cords on the fetal surface. In this case a breakdown of the partition between the two amniotic sacs due to pulsation of closely approximated cords could not have been the cause of these twins occupying the same amniotic sac.

Summary

A review of the reported cases of monoamniotic twins is given. Including the case reported in this article there have been 166 cases of monoamniotic twins in the world's medical literature, with both twins surviving in 40 cases.

Theories regarding the etiology of this condition are given. The development of twins on a single germ disc, as illustrated by Corner, seems best to explain the origin of monoamniotic twins.

I wish to express my appreciation to Dr. George W. Corner for his interest and for his permission to use the illustration on single ovum twinning.

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UTERINE HYPERTROPHY IN THE PRESENCE OF ANDROGEN-PRODUCING ADRENAL TUMOR

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THE cause of uterine hypertrophy is not known. The usual experience in experimental studies has been a regression of female sex organs in the presence of large amounts of androgens. Because of these facts the following unusual case report is submitted.

Case Report

History.—The patient was a 32-year-old white, married, American woman, gravida 0, admitted on Aug. 23, 1955, with the history of virilization for eighteen years. Her birth and childhood were normal. She had a normal sequential pubescence culminating in menarche at 11 years of age. Thereafter she had regular menstrual periods every twenty-eight days, of four days' duration, for three years. At 14 years of age she developed amenorrhea, accompanied by the appearance of facial hair and increased bodily strength. By 17 years of age she was shaving her face every other day, and had acne, greasy skin, and increased body hair. Her voice deepened in her twentieth year, and by this time she was shaving her entire body once a week. At 21 years of age she was married and claimed normal libido. No contraception was employed but no pregnancies occurred. Her local physician performed a pelvic laparotomy the next year. She related that he found and removed a "pin-head sized" tumor from the right ovary but left the ovary itself in place. No other abnormalities were described to the patient. Beyond the patient's history, no details of this operation have been obtainable. No improvement of the patient's condition resulted from the operation. By 27 years of age her acne had become much worse and she was experiencing temporal recession of the scalp hair. An episode of bilateral flank pain with urinary tract infection and passage of "gravel" occurred at 29 years of age. Four to six months prior to her first visit to Duke Hospital she had bilateral lower abdominal pain of a dull, aching nature, and lost 10 pounds. There had been no wasting, backache, easy bruising, known glycosuria, or hypertension.

Physical Examination.—The blood pressure was 150/100, temperature 37° C., pulse 88, and respirations 18. She had a very android habitus, with a low voice, heavy musculature, and thin subcutaneous fat padding. Her skin was thick, greasy, and oily, with diffuse acne over the face, chest, and back. There was temporal recession of the heavy, coarse scalp hair, and she had dense, black, shaved hair over the entire body, especially the lower face (Fig. 1). The breasts were well developed, Stage IV, with definitely palpable breast tissue, and good nipple and areolar development. The abdomen had a healed, midline surgical scar extending upward from the symphysis pubis to just below the umbilicus. A midline, suprapubic, nontender, mobile mass was palpable abdominally. Pelvic examination disclosed an android hair pattern and a moderately enlarged clitoris. Severe vaginitis was present. On bimanual examination a 10 cm. sized mass was found which extended more

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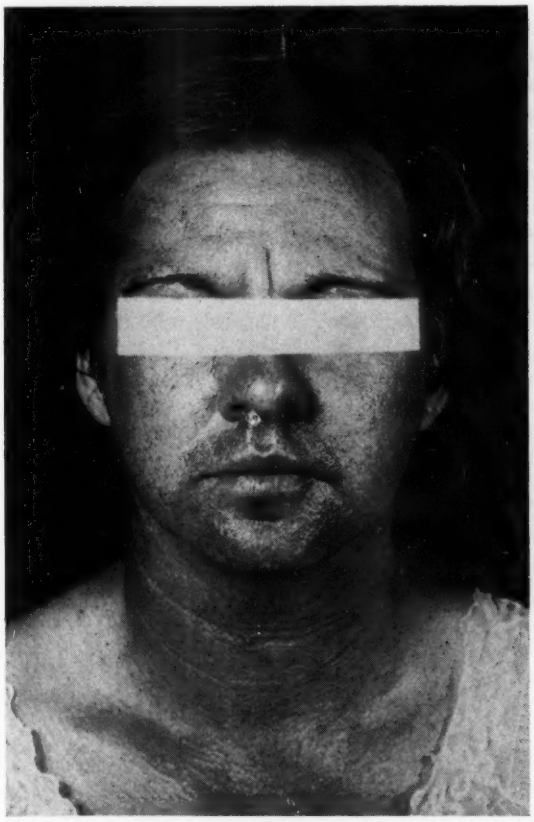


Fig. 1.—Patient's face 24 hours after shaving. Note receding hairline, thick, greasy skin, and heavy beard.



Fig. 2.—Gross specimen, uterus, external surface.

to the right than the left, but was essentially midline. It was indistinguishable from the uterus. Neither ovary was palpable and no separate adnexal masses were palpated. The remaining physical examination was negative.

Pertinent laboratory findings were: red blood count 6.11 million, hemoglobin 18.6 Gm., hematocrit 53.2, white blood count 8,500 with normal differential. Bone marrow study showed erythroid hyperplasia. Urinalysis was negative. The blood nonprotein nitrogen was 37 mg. per cent; serum sodium 147 meq. per liter; serum potassium 4.0 meq. per liter; serum calcium 9.9 mg. per cent; serum phosphorus 2.7 mg. per cent. Results of the glucose tolerance test were: fasting, 90 mg. per cent; ½ hour, 165 mg. per cent; 1 hour, 230 mg. per cent; 2 hour, 150 mg. per cent; 3 hour, 90 mg. per cent. The serological test for syphilis was negative. Roentgenograms of the skull were negative; abdominal flat film showed a pelvic mass; chest film showed slightly increased heart size. (Intravenous pyelograms were done at another hospital two weeks before the patient's admission to Duke Hospital, and reported as negative. They were not repeated here.) Data on 17-ketosteroid and 17-hydroxycorticoid excretion in the urine are given in Table I.

TABLE I. URINARY EXCRETION OF 17-KETOSTEROIDS AND 17-HYDROXYCORTICOIDS OF PATIENT*

DATE	17-KETOSTEROIDS IN MG./24 HOURS	17-HYDROXYCORTICOIDS IN MG./24 HOURS
8/25-8/26	158.0	13.1
8/26-8/27	240.2	8.3
8/27-8/28 ACTH†	155.2	19.2
8/28-8/29	110.8	10.3
9/18-9/19 (postoperative)	1.2	4.0

*Normal values for this laboratory in the adult female are: 17-ketosteroids, 4-18 mg./24 hours, 17-hydroxycorticoids, 5-15 mg./24 hours.

†When the 8/27-8/28 collection was begun, an intravenous infusion was started consisting of ACTH, 25 I.U., in 500 ml. of 5 per cent dextrose in distilled water. This mixture was infused over the first eight hours of the collection.

Preoperative Diagnostic Impressions.—On the basis of the findings reported, it was felt that the most likely diagnostic possibility was an adrenal tumor, but that adrenal hyperplasia and ovarian tumor could not be completely ruled out. The pelvic mass was thought to be an enlarged uterus, but with the history of probable previous right ovarian pathology, and extension of the mass to the right side of the pelvis, ovarian tumor remained as a definitely possible, though unlikely, cause of the symptom complex. With the marked virilization this patient showed, plus the very high urinary 17-ketosteroid excretion, uterine leiomyomas were considered highly unlikely. It was decided that the pelvis would be approached first for several reasons: (1) Ovarian pathology could not be excluded. (2) The mass was of sufficient size so that removal would probably be necessary despite other pathology, and we preferred to do major surgery on a patient who had not had previous adrenal surgery. (3) The suprarenal areas could be explored at the time of lower abdominal incision. If a tumor was discovered by palpation in either adrenal area, the site of approach for adrenal surgery would be determined.

Operative Findings.—On the sixth hospital day a pelvic laparotomy was performed without preoperative steroid medication. The pelvic mass was found to be a symmetrically enlarged uterus about 12 cm. in diameter, freely movable and not attached to surrounding structures. The right ovary was absent. The left ovary appeared somewhat atrophic, but was otherwise not unusual. Exploration of the upper abdominal cavity revealed a soft, semisolid, globular, 8 cm. mass above the superior pole of the right kidney. It was mobile to palpation and felt encapsulated. The left adrenal could not be palpated. The operative impression of the pelvic mass was intramural leiomyomas, and because of the great enlargement of the uterus a total hysterectomy was performed. The remaining ovary was left in place. The patient had an uneventful postoperative course, except for slight tachycardia and moderate psychic upset. Eight days later the adrenal mass was removed without difficulty through a transthoracic incision.

Pathologic Report and Diagnosis.—The uterus measured 16 by 12 by 9 cm. in greatest dimensions and the estimated weight was 1,200 grams (Fig. 2). Multiple cuts failed to demonstrate a gross tumor mass. The myometrium was thick and rubbery in consistency and appeared somewhat fibrous grossly. On microscopic section the report was: "The myometrium is diffusely enlarged. Differential staining techniques reveal that the enlargement is due to hypertrophy of smooth muscle. There is a normal amount of fibrous tissue interspersed throughout the smooth muscular strands" (Figs. 3 and 4). The endometrium was found to be atrophic, with the stroma replaced by well-differentiated fibrous tissue, and the glands quite scarce (Fig. 5). Diagnosis: "Chronic endocervicitis. Atrophic endometrium. Idiopathic hypertrophy of uterus." The right adrenal mass proved on pathologic examination to be a rather pleomorphic cortical adenoma that showed no areas of invasion of the capsule (Fig. 6).

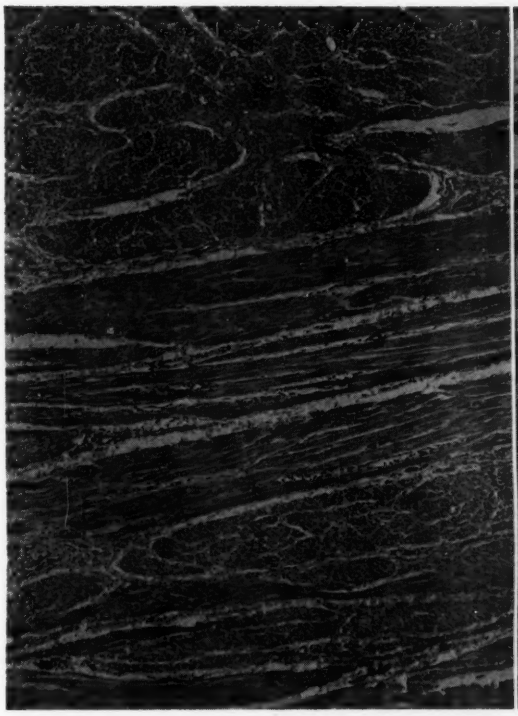


Fig. 3.

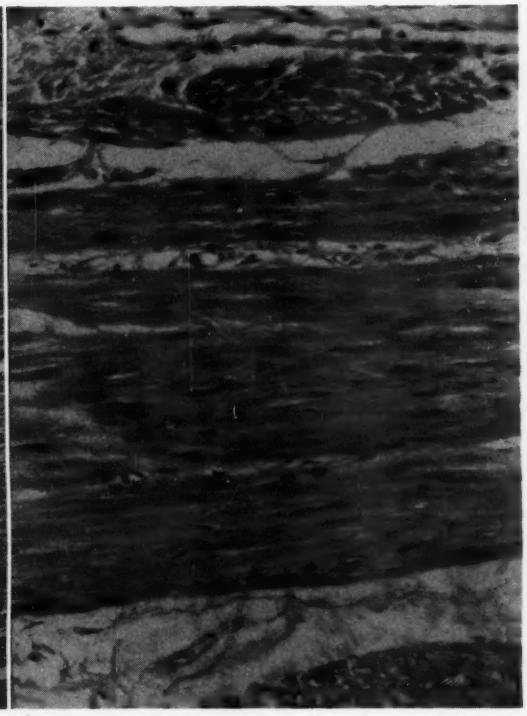


Fig. 4.

Fig. 3.—Photomicrograph of myometrium under low power. Large bundles of hypertrophied muscle fibers are seen, interspersed with loose collections of fibrous tissue. (×69; reduced ⅕.)

Fig. 4.—Photomicrograph of myometrium under high power. Note large, prominent nuclei. (×237; reduced ⅕.)

Further Course.—The patient received 200 mg. of cortisone intramuscularly daily for two days before adrenal surgery and then the dosage was gradually reduced postoperatively. ACTH was given also, in the last few days of cortisone administration, in diminishing doses. She had a marked psychic upset after operation, but her course was otherwise uneventful, and she was discharged on Sept. 22, 1955.

The patient was readmitted on Oct. 20, 1955, because of marked lassitude, depression, and diarrhea. Much of her depression was on a psychiatric basis, but she was also found to have abnormally low urinary excretion levels of both 17-ketosteroids and 17-hydroxycorticoids. This was contrary to our usual experience with 17-ketosteroid-excreting tumors

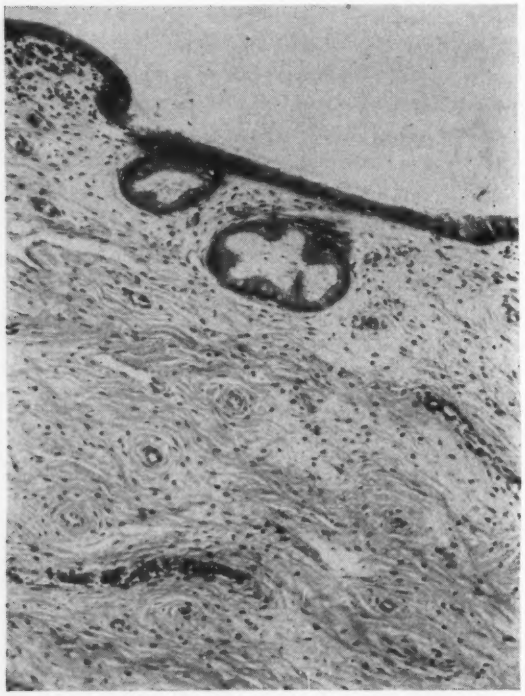


Fig. 5.—Photomicrograph of endometrium. The stroma is entirely replaced by mature fibrous tissue, and the glands are scarce and appear inactive. (×119, reduced ⅙.)

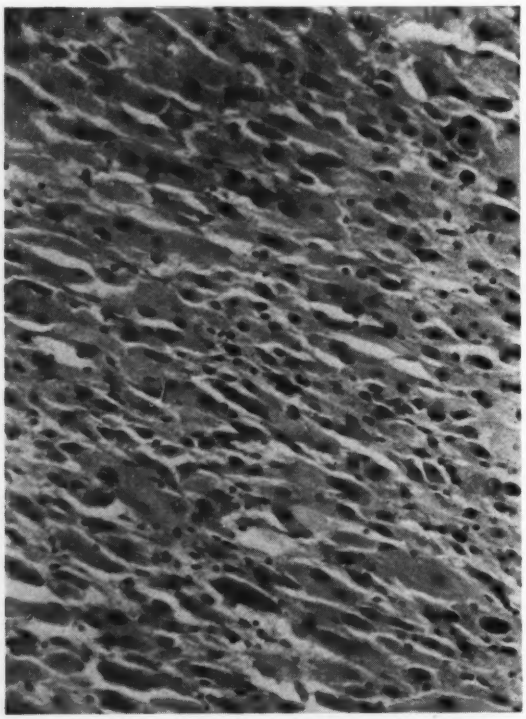


Fig. 6.—Photomicrograph of right adrenal cortical adenoma. There is some irregularity of nuclei in size, shape, and staining. (×237; reduced ⅙.)

of one adrenal, which usually do not have a markedly suppressive effect upon the contralateral adrenal. Her steroid-excretion levels rose to normal with ACTH injections (ACTH Gel, 20-25 I.U. daily intramuscularly), and most of her symptoms disappeared. There was some psychiatric overlay remaining at the time of her discharge on Nov. 8, 1955.

Comments

The uterine hypertrophy in this patient is most puzzling in the presence of her markedly high androgen levels. The hypertrophic response of skeletal muscle to androgen stimulation is well known. Indeed, this response is used in one method of bio-assay of testosterone.[1, 2] No involvement of smooth muscle under these circumstances has ever before been noted at this hospital, however. A survey of the recent literature by one of us failed to disclose any similar instance. Lipschütz,[3] in his experimental work with steroids in animals, found that androgens tended to decrease the size of tumors in female animals to which they were administered. However, he employed androgens only after previous use of massive doses of estrogens. Few cases of virilizing syndromes of as long standing as this patient's can be found in the literature. Regardless of duration, none was found with a picture similar to this instance in regard to uterine response. We have no explanation for the uterine hypertrophy encountered in this patient.

Summary

A case report is present of a 32-year-old woman with a virilizing syndrome due to adrenal cortical adenoma, and complicated by idiopathic uterine hypertrophy.

A brief discussion of muscular tissue response to androgens is given. No explanation for this singular behavior of smooth muscle is offered.

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CEREBRAL HEMORRHAGE AS A MANIFESTATION OF THE SICKLE-CELL PHENOMENON

Case Report With Autopsy Findings

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SICKLE-CELL anemia, the homozygous state of sickle-cell disease, has long been known to cause severe clinical manifestations. Bauer[3] in 1940 was one of the first to point out that clinical manifestations of sickle-cell disease could be present without anemia and that routine sickle-cell preparations should be done on all Negroes in order to avoid many erroneous diagnoses. More recent reports, however, have pointed out that vascular occlusions leading to clinical symptoms may occur in those harboring the sickle-cell trait.

In the past few years new variants of sickle-cell disease due to the discovery of new abnormal hemoglobins have been added to the literature in increasing numbers. The broadening concept and the clinical features of the various genetic variants are admirably discussed by Chernoff[4] and by Smith and Conley.[5] By electrophoretic determination of hemoglobin patterns, many cases of the so-called sickle-cell disease without anemia can be properly classified as to their exact type of hemoglobin abnormality. With new hemoglobins C, D, E, G, and H already described, it is very likely that more variants will be found in the future. Central nervous system manifestations appear to be frequent and often severe in the variants.

The following case is presented as an example of cerebral hemorrhage in a postpartum Negro woman who we believe had sickle-cell disease without anemia.

This 27-year-old Negro woman, para viii, was admitted to the United States Army Hospital at Fort Ord, California, on March 8, 1954, on the eighth postpartum day because of severe headache. On Feb. 25, 1954, the patient was delivered of a twin pregnancy under nitrous oxide anesthesia without complications. At no time during her prenatal course or during her hospital stay on the admission for delivery did the patient show an elevated blood pressure, and at no time was there albumin in the urine. The infants remained well. The patient developed a headache on the morning of March 7, 1954. The headache persisted throughout the day, and at approximately 1:15 A.M. on March 8, 1954, she was admitted to the hospital with convulsions which were considered by the obstetrician on call to be eclamptic in origin.

Physical examination on admission revealed an obese Negro woman in active clonic and tonic convulsions. Her pulse was 82, blood pressure 150/100, and temperature was 99.6° F. by rectum. The left border of the heart was percussible in the anterior axillary

line. A faint systolic blow was heard at the apex. The spleen was palpable 2 finger-breadths beneath the left costal margin and the liver was palpable 3 cm. below the costal margin in the right midclavicular line.

Laboratory Data.—On Nov. 22, 1953, results of urinalysis showed the urine to be yellow clear, acid, with a specific gravity of 1.010, and negative for albumin and sugar. The leukocyte count was 8,200, with 75 neutrophils, 23 lymphocytes, and 2 eosinophils. The hemoglobin was 14.4 Gm. In January, 1954, results of urinalysis showed the urine to be yellow clear, acid, with specific gravity of 1.005, and negative for albumin and sugar. The serologic test for syphilis was negative. On March 8, 1954, the leukocyte count was 8,200, hemoglobin 14 Gm. with 80 neutrophils, 18 lymphocytes, 2 eosinophils. The test for erythrocyte sickling unfortunately was not performed. Nonprotein nitrogen was 25 mg. per cent and uric acid was 2.4 mg. per cent. Results of urinalysis showed the urine to be yellow clear, acid, with specific gravity of 1.008, and negative for albumin and sugar. A lumbar puncture was performed without difficulty and without trauma. The spinal fluid was grossly bloody and the manometer reading showed a pressure of more than 610 mm. of water. The spinal fluid showed an erythrocyte count of 660,000 with a hemoglobin of 1.7 Gm. At 11:00 A.M. on March 8, all the reflexes were absent; there was no pupillary reaction to light and no response to pain. Respiratory embarrassment ensued and the patient was placed in a respirator. Her condition rapidly deteriorated and she died two hours later.

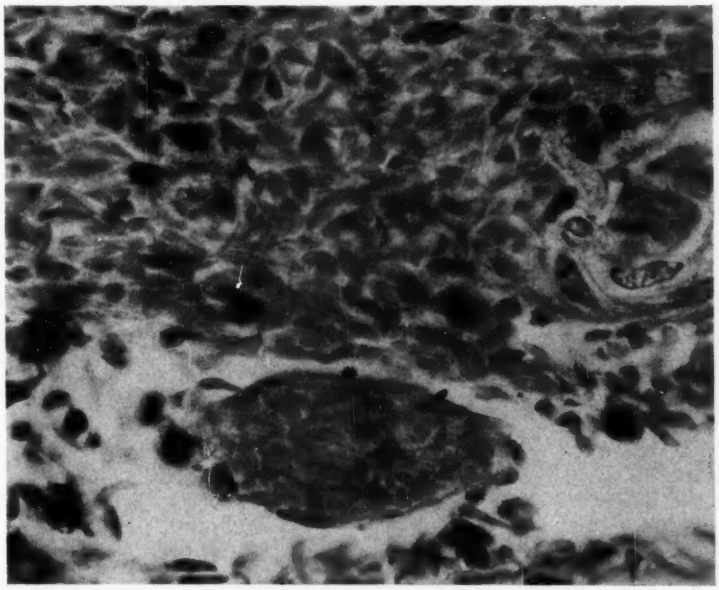


Fig. 1.—Photomicrograph of brain showing sickled erythrocytes within blood vessels and in area of hemorrhage. (Hematoxylin and eosin. ×900; reduced ⅓.)

Necropsy Findings.—At necropsy, the heart was found to be enlarged, weighing 450 grams. The liver weighed 2,640 grams, and the spleen 580 grams. Severe subarachnoid hemorrhage which was most pronounced over the right frontal lobe was evident. Upon horizontal sectioning into the brain, a blood clot which measured 5 by 2 cm. was encountered in the region of the anterior horn of the right ventricle. At the level of the genu of the corpus callosum, the zone of hemorrhage measured 6.5 by 3 cm. and disrupted the right cerebral cortex and underlying white matter. Careful inspection of the vertebral, the basilar, the common carotid, and the anterior, middle, and posterior cerebral arteries showed no evident occlusion, atheroma, aneurysm, or perforation.

Microscopic examination of the tissues revealed within the hilar lymph nodes foci having the histology of sarcoid. Similar epithelioid-cell lesions were encountered in the liver. Moderate to very severe congestion of the red pulp was present in the spleen.

Hemorrhage had occurred in the peripheral portions of many lymphoid follicles. Sections of the brain revealed over the right frontal lobe a moderate amount of apparent fresh subarachnoid hemorrhage. Hemorrhage into the cerebral tissue was noted in the areas described in the gross. The striking findings within small cerebral vessels in formalin-fixed sections were the presence of densely packed erythrocytes with elongated sickle shapes and pointed ends (Fig. 1). Similar sickled erythrocytes were seen in vessels in the formalin-fixed tissue from other organs.

Anatomic Diagnoses.—(1) Hemorrhage, intracerebral, frontal lobe with communication with the intraventricular and subarachnoid space; (2) sarcoidosis, lungs, liver, and lymph nodes; (3) cardiac hypertrophy (450 grams, etiology undetermined); and (4) sickle-cell disease.

Comment

This case is one of a 27-year-old Negro woman who ten days post partum developed headaches followed by coma and convulsions with death thirteen hours after hospitalization. The autopsy findings of significance were the presence of cerebral hemorrhage, cardiac hypertrophy with no anatomic etiological explanation, and splenomegaly and hepatomegaly with the lesions of sarcoid and the presence of sickled erythrocytes within the body tissues. In addition, changes in the spleen which by some are considered pathognomonic of sickle-cell disease were noted. It is believed that the sickling phenomenon played a direct role in the etiology of the cerebral hemorrhage. This case poses an interesting problem as to whether it should be classified as the sickle-cell trait or as sickle-cell anemia. It is generally stated that complications do not arise from the trait. However, recent publications have pointed out that such complications may occur. The age of the patient without preceding evidence of sickle-cell disease, the absence of any significant anemia, and the absence of histologic evidence of long-standing hemolysis forces one to the conclusion that this represents a case of sickle-cell trait complicated by cerebral hemorrhage in a postpartum Negro woman.

While sickle-cell anemia with pregnancy is quite rare,[2] pregnancy with sickle-cell trait was present in 79 per cent of 2,011 Negro patients reported by Adams.[1] While fertility is not affected by sickle-cell anemia, the occurrence of pregnancy is by necessity rare since patients with sickle-cell anemia usually die at an early age. As in sickle-cell anemia, pregnancy is a definite hazard to the patient with the sickle-cell trait. Close observation during the pregnancy and every effort to avoid anoxemia of any degree during delivery are mandatory. Severe anemia should be treated by transfusion and every precaution should be taken to avoid infections.

Summary

1. This case is one of cerebral hemorrhage occurring in a Negro woman patient possessing the sickle-cell trait.

2. The necessity for routine sickle-cell preparations on Negro obstetrical patients is apparent.

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ENDOMETRIOSIS OF THE VULVA DURING PREGNANCY*

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EMIL NOVAK,[6] in the third edition of his *Gynecologic and Obstetric Pathology*, in 1952, described endometriosis of the vulva as having been reported in only about a dozen instances. In 1953, Goldfarb[3] reported the fifteenth case, and, in 1954, Duson and Zelenik[1] reported the sixteenth case. Among the 16 cases only about 2 could be found that occurred during pregnancy. Since endometriosis during pregnancy is so rare, an additional case is reported.

The patient, H. P., was a 31-year-old woman, married for 6 years. Her first menstruation occurred at the age of 12½ years. The periods occurred every 28 days, with a duration of 3 to 4 days, and cramps till the birth of her first child. The report of the first delivery 3½ years before her present admission stated that the right occipitoposterior position of the head had been rotated by forceps into occipitoanterior position. A right mediolateral episiotomy was made, but a second-degree tear of the perineum almost down to the sphincter was produced. Both were repaired.

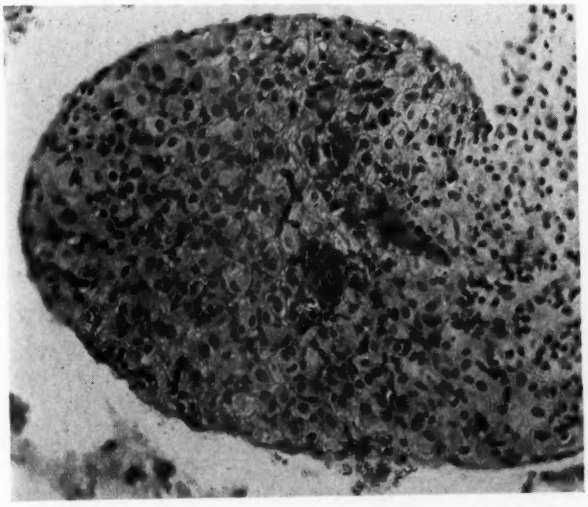


Fig. 1.—Magnification of the polypoid outgrowth. Note massive decidual change of stroma.

The patient was seen for the first time at about the seventh week of her second pregnancy. She appeared entirely normal, except for a mild cervical erosion and a soreness on top of a scar from the median second-degree tear sustained during her first delivery. The tender area measured 2 by 1 cm. in size, was reddish, and resembled granulation tissue, slightly elevated above the surface of the vulva.

Since conservative treatment was not satisfactory, the whole area was excised. The specimen, according to the report of Dr. Motyloff, chief pathologist of Woman's

*Presented at the Stated Meeting of the Clinical Society of Sydenham Hospital, New York City, May, 1955.

Hospital, presented an ulceration lined by excrescences of decidua showing apparently a decidual change of connective tissue elements of granulation tissue. In other instances there was columnar epithelium covering the fungating projections of ectopic decidua, suggestive of a possible endometriosis of this region with decidual change. There was no evidence of malignancy. The diagnosis was endometriosis of the vagina, with extensive decidual change.

Re-examination disclosed no further sign of endometriosis of the vagina, or of the cervix, or of the rectovaginal fascia. By thorough review of the patient's history it was found that right after her first delivery a sore spot in the same region had been treated for several weeks. About 2 years later, the patient observed that 2 days before her menstruation she had bled momentarily. During the following 18 months, till the beginning of her present pregnancy, she always could be certain that 2 days after this minute bleeding her menstruation would start.

Comment

The visible endometriosis showed the rare decidual reaction of pregnancy that is described in only a few instances. The clinical and histological findings just described corroborate the experimental result when Harbitz[4] studied endometriosis by graft on rabbits in 1934. They concur with the opinion of Gardner,[2] who reported to the Sixth American Congress on Obstetrics and Gynecology, in Chicago, December, 1954, that "the heterotopic endometrial-like tissue of endometriosis responds to hormonal stimuli in the same manner as the endometrium lining the cavity of the uterus . . . it shows gestational effects during pregnancy."

Bleeding 2 days before menstruation may be a symptom leading to the early diagnosis of perineal endometriosis. McLeod[5] reported a similar observation in 1946.

Summary

In a scar from a previous second-degree median tear, unencapsulated endometriotic tissue with decidual reaction was found, 2 years after delivery, during a new pregnancy.

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REMOVAL OF A NEEDLE FRAGMENT LOST IN THE PERINEUM DURING EPISIOTOMY REPAIR

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EPISIOTOMY repair is apparently a safe procedure; although it is done thousands of times daily, reports on complications are rare. Concerning needles lost in the perineum, a search of recent American literature yielded only one passing remark by Willis.[1]

A case in which a needle broke during repair of an episiotomy, was lost in the tissues, and was removed later by an apparently new method therefore seems worth reporting.

Fig. 1.

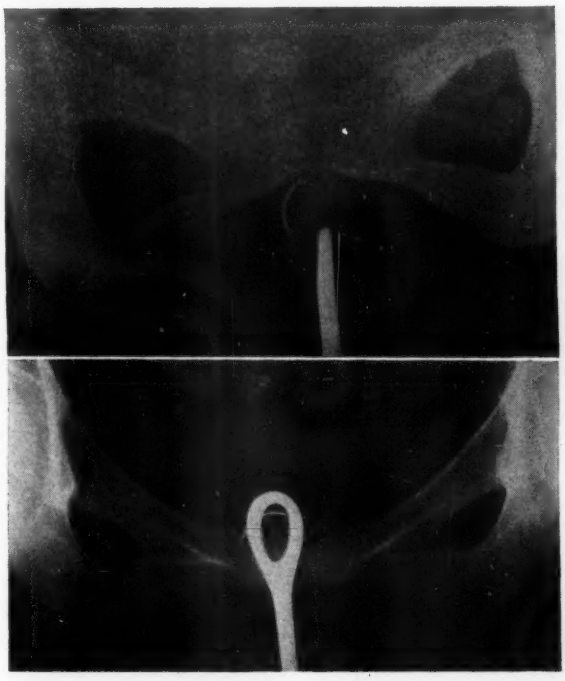


Fig. 2.

Mrs. E. G. M. (V. B. H. 55-4386), aged 24, was delivered easily of her first child on Sept. 29, 1955, under low spinal anesthesia. She had a midline episiotomy and a low forceps extraction. During the episiotomy repair, the needle broke and the free fragment disappeared in the tissues. The field was bloody, and the tissues were edematous. For about ten minutes I tried to find the needle fragment, but could neither see nor feel it. Finally I gave up and completed the repair. An x-ray picture, taken the next day, showed the needle fragment plainly (Fig. 1). The patient left the hospital on Oct. 1, 1955, having

been informed of the mishap and of my plan to remove the foreign body after the tissues had returned to their normal condition. She was seen regularly at the office, and her postpartum course was normal.

On Nov. 8, 1955, all swelling was gone and the episiotomy incision well healed. Neither by vaginal nor by rectovaginal palpation could the needle fragment be located. On Nov. 9, 1955, the patient re-entered the hospital. In the x-ray room she was given low spinal anesthesia. Under fluoroscopic vision a sponge-holding forceps was inserted, one ring into the vagina and the other ring into the rectum, and manipulated until the shadow of the rings encircled most of the shadow of the needle fragment (Fig. 2). Then the forceps was closed and locked. The patient was taken to the operating room, placed in lithotomy position, and a Radcliff spreading speculum was inserted. The small area of the rectovaginal septum clamped between the rings *had to contain the foreign body.* The vaginal mucosa was incised within the ring placed vaginally and the needle was soon found and removed. The closed forceps not only identified the site of the foreign body, but also produced hemostasis. The wound was closed with a few fine surgical gut sutures. The patient left the hospital the next day. She was seen in the office on Nov. 17, 1955; she was well.

This method of locating, "arresting," and removing a small metallic foreign body is simpler than x-ray methods using geometric projections and landmarks on body surfaces. It is usable only for foreign bodies in comparatively thin and accessible tissue layers (rectovaginal septum, tongue, cheek, penis, scrotum).

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Editorial

Routine Laboratory Work

As teacher, consultant, and Associate Examiner, I have noted that a request for routine chemistry in obstetric and gynecologic patients is usual with students and doctors studying any sick patient or any patient presenting an obscure diagnosis. The term "routine laboratory or chemistry" is without meaning unless someone has established certain procedures for *particular* conditions. While routine laboratory work may mean myriads of approaches, routine chemistry may mean one or hundreds of determinations.[1, 2, 3, 4] Usually several determinations will aid in the diagnosis, but chemical analysis alone is rarely sufficient to establish a definite diagnosis. Thus determinations such as high blood N.P.N., B.U.N., and bilirubin may be caused by more than six conditions or diseases. While the tendency among students and candidates is to anticipate levels well above the standard normals, low levels are often considered as being within normal limits whereas such low levels may be more or less specific in certain diseases.

Accurate hematology is indicated in all patients. While the hemoglobin determination is accurate when properly done, it cannot be compared with the hemoglobin determination done by various laboratories since the methods may be quite different. The hematocrit is presently considered to be much more accurate than the erythrocyte count and also more specific than the standard hemoglobin determination. Since there are many methods of hemoglobin determination, the accuracy varies with the method used. The determination of the hematocrit appears to be a much more desirable method since there is only a single satisfactory method of determining hematocrit and this method has the advantage of repeated reproducibility.

The leukocyte and differential counts and possibly the sedimentation rate (properly corrected) are indicated in patients with fever or with undiagnosed conditions. Here, too, two sets of normals must be established since the leukocyte count and the sedimentation rate are normally increased during pregnancy over the standard nonpregnancy levels.

The platelet count is of value when properly done using proper phase optics. It should be considered as only a part of the various determinations in assaying the coagulation mechanism. These various other determinations are the clotting, bleeding, and prothrombin times and plasma fibrinogen and they should be performed in all patients with a bleeding tendency.

The pre- and postoperative care of patients who are losing body fluids as a result of vomiting, diarrhea, or fistula, or who are oliguric or anuric for any reason, necessitates at the minimum serial hematocrits to ascertain the degree of hemoconcentration or hemodilution and its changes. Serum chloride, sodium, and potassium determinations should be made daily during the clinical course of the disease and proper therapy instituted to correct excess or deficit. Serum bicarbonate and pH determination may also be necessary. A full knowledge of the significance of low levels and high values for each of these ions is important. Simultaneous high and low levels of serum anions and cations may coexist in a given clinical condition. For example, the hyperkalemia of acute renal failure is often associated with hyponatremia in the severely edematous pre-eclamptic patient. Where there is an excessive loss of anion (chloride by vomiting of gastric juice, bicarbonate by intestinal fistula) the serum sodium, chloride, and CO_2 content should be determined because of the likelihood of compensated or uncompensated alkalosis or acidosis. But these studies must also be correlated with the clinical condition of the patient and not only with a table of standard figures. This becomes particularly true where hypochloremic metabolic acidosis may produce the same set of chemical readings as may be present in an uncompensated alkalosis. If the latter condition is present, a serum pH is indicated; but such a procedure is not practicable except with the use of a very special research pH meter, operating under standard conditions and being carried out by a well-trained technician.

The presence in the urine of ketone bodies in the absence of diabetes mellitus or severe chronic nephritis is not characteristic of an acidosis, meaning a low CO_2 content and low pH. As a rule, the pH is normal in these patients and the CO_2 varies from 25 to 28 millimols per liter and no parenteral sodium lactate or bicarbonate is necessary.

The blood N.P.N. comprises the total nonprotein nitrogen in the blood and this determination requires less time and in most laboratories is more accurate than the blood B.U.N. determination. Both values will be increased in the presence of oliguria and anuria from any cause, as well as in patients with advanced acute or chronic nephritis. The blood uric acid is one of the first of the nonprotein constituents to be elevated in cases of temporary or permanent renal impairment; by the time that it has become significantly elevated, so many other abnormal patterns have made themselves apparent that it is then unnecessary to do this determination.

Serum calcium and phosphorus determinations are not commonly made; when they are, a serum protein analysis should also be obtained for free and ionized calcium calculation.

Plasma fibrinogen should be determined as fibrinogen or fibrin wherever there is a bleeding tendency and in all cases with extensive or repeated phlebothrombosis. Not only should the calculation of this fraction be determined but it should be compared with the total proteins. To be of real significance, particularly in an episode of defibrination, the determination should be made electrophoretically.

There are many other blood determinations, some of which are necessary in selected cases for the final diagnosis.

Urine chemistry, except for protein and reduction tests, has been neglected. In the patient with low serum chlorides the addition of a 1 per cent acidified silver nitrate solution to a urine specimen will demonstrate immediately whether or not the serum chloride may be normal. The tendency has been perpetuated, however, for urine chlorides to be utilized as being synonymous with urinary sodium. While a relationship exists, it is by no means proportionate and should not be considered as the only means of calculating and in maintaining accurate electrolyte balance. The exception occurs in the patient who has marked renal impairment from chronic nephritis or in the recovery phase after lower nephron nephrosis or mercuric chloride poisoning.

Copper reduction in the urine may be due to the dextrose or one of several other sugars. Lactosuria is rare even in pregnancy. The urine should be obtained after an all-night fast and if it shows reduction then a determination of the 24 hour reducing power and the causative sugar should be determined. The presence of one or more grams of reducing substance in a 24 hour urine specimen is always abnormal. A fasting blood sugar determination and possibly a glucose tolerance test should be obtained.

Many of the books[1, 2, 3, 4] on clinical chemistry contain values for minimum, maximum, and mean concentrations for the usual urine and blood constituents.

No routine chemistry or book will solve all problems of diagnosis and treatment. No set of values necessarily fits all clinical problems. In the final analysis, laboratory work cannot be considered an adequate substitute for clear-cut clinical appraisal. Laboratory work is really an adjunct in diagnosis. The important considerations should be a complete history, complete examination, and a frequent review and analysis of the clinical situation. Very often multiple clinical possibilities are suggested to the consultant by simply reading the chart, but many of these are ruled out immediately and the true diagnosis pinpointed when the patient is seen. Only the intelligent use of routine laboratory work and routine clinical methods will most frequently produce miracles.

W. J. D.

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Reviews and Abstracts

EDITED BY LOUIS M. HELLMAN, M.D., BROOKLYN, N. Y.

Review of New Books

Anesthesia for Obstetrics—Labor—Delivery—Infant Care. By R. A. Hingson, and L. M. Hellman. 344 pages with 122 figures. Philadelphia, 1956, J. B. Lippincott Company. $12.50.

Two authorities, one eminent in the field of anesthesiology and the other in obstetrics and gynecology, have produced a book which describes the present-day applications of analgesia, amnesia, and anesthesia to obstetrics.

The opening chapter introduces the subject in broad perspective and states the basic theme of the text: "the development of teamwork between obstetrician and anesthetist in the management of maternal and infant comfort and safety." Characteristics of good and safe anesthesia and analgesia are enumerated and basic principles for the various agents are explained by a number of full-page illustrations.

After a fascinating chapter devoted to a historical survey of the subject, anatomic and physiologic considerations are dealt with. The problem of vomiting during anesthesia and delivery is clarified. A chapter on techniques is devoted mainly to "frontal lobe block," "total brain block," and "regional nerve block." Under the heading "Psychological Principles of Pregnancy and Delivery," considerable space is devoted to the parturient's evaluation of drugs, techniques, and doctors. This evaluation is based upon the Baltimore Obstetric Anesthesia Study and is very enlightening.

"Control of Pain in Maternal and Fetal Complications" is an evaluation of the best anesthetic agents for use in such conditions as heart disease, toxemia, and obstetric complications. Virginia Apgar contributes a sound and practical chapter on "Maternal and Infant Safeguards." The final chapter is devoted to the "Organization of Obstetric Anesthesia on a 24-Hour Basis," which is an important problem in many hospitals throughout the country.

Only a few chapters have an adequate bibliography. In several chapters in which many workers are mentioned, there are no references. The lack of a bibliography for the historical chapter is unfortunate.

In general, the illustrations are clear and valuable. Pictures of the bony pelvis, the muscles of the pelvic floor, and abdominal palpation might well be omitted. There are no illustrations for local or paravertebral anesthesia.

The book is well printed and there is an adequate index. It should be of great value to specialists in both fields, including those in training, both on the graduate and postgraduate level.

CLAUDE EDWIN HEATON*

Mechanisms of Congenital Malformation. Proceedings of the Second Scientific Conference of the Association for the Aid of Crippled Children, June 15 and 16, 1954, S. R. M. Reynolds, Chairman. 137 pages with 50 illustrations. New York, 1955, Association for the Aid of Crippled Children. $3.00.

This small volume of 130 odd pages contains the proceedings of the Second Scientific Conference held under the auspices of the Association for the Aid of Crippled Children.

*Because the editor of Reviews and Abstracts is coauthor of *Anesthesia for Obstetrics*, an exception has been made to the editorial policy in regard to the signing of book reviews.

Forty-three distinguished American and foreign scientists participated in the Conference, of which Dr. S. R. M. Reynolds was the chairman. The title of the work, "Mechanisms of Congenital Malformation," hardly does justice to either the breadth or the scope of the meeting, which was divided into three main sections, as follows: (1) physical, chemical, and sociological aspects of the fetal environment; (2) the placental barrier, and (3) the fetus.

There is obviously little space specifically given to congenital malformations except in the first section. In this section, of particular interest are the charts of Dr. James Walker of Aberdeen. These show the marked effect of social status on fetal deaths and congenital malformations and prematurity. In the second section, there were two interesting discussions on the impermeability of the placenta to proteins and fat. The final section contains a beautiful discussion of fetal hemoglobin. This includes not only the specific differences between maternal and fetal hemoglobin, but also concerns itself with the dissociation curves and the question of the influence of pH on the affinity of the fetal hemoglobin for oxygen.

As can be seen from this brief outline of the Conference, its scope was extremely broad and included many interesting subjects. Typical of many such conferences, no one subject was thoroughly covered. This is not meant as criticism of the Conference for it touches clearly, concisely, and in a modern way upon many problems dealing with fetal existence. If final answers are not here, the reason is that they are for the most part unknown. Indeed, this volume is a stimulus for much thought and additional research.

Attuali Orientamenti Sulla Terapia Ormonale in Ginecologia. By F. Marchesi. 163 pages. Torino, 1955, Edizioni Minerva Medica. 1500 L.

This monograph on hormone therapy is written with clinical orientation. The first section discusses methods of determining hormone function (such as endometrial biopsy and cervical smear), the aims of hormone therapy (such as stimulation and substitution), and a description of the various hormone preparations commonly used in Italy, based on the producing gland. The second section is devoted to the application of the foregoing to various types of menstrual aberrations, including primary and secondary amenorrhea, hypo- and hypermenorrhea, oligomenorrhea, functional bleeding, and dysmenorrhea. An analysis of the physiology of each clinical disturbance is given. The therapeutic use of deficient or antagonistic hormones is discussed.

Maternal Emotions: A Study of Women's Feelings Toward Menstruation, Pregnancy, Childbirth, Breast Feeding, Infant Care, and Other Aspects of Their Femininity. By Niles Newton. 150 pages. New York City, 1955, Paul B. Hoeber, Inc. $3.00.

This study, written by a research psychologist familiar with the obstetrical field, is based on data collected through single interviews with 123 mothers while they were with their infants in rooming-in wards of the Jefferson Medical College Hospital, Philadelphia. The interview, on the first or second day post partum, utilized standardized questions regarding menstruation, pregnancy, childbirth, breast feeding, rooming-in care of the baby, envy of men, and other aspects of the female role. Medical case records contributed additional data.

The chief conclusions are as follows: (1) There is a marked relationship between difficulty of menses, pregnancy, labor, and breast feeding, and these difficulties are related to difficulties in the woman's picture of the female role and herself as a woman. (2) Women in our culture have lost much of their previous prestige value as equal partner and have gained little prestige in their role of mother and homemaker. (3) Too much cultural emphasis has been placed on the burdensome quality of pregnancy and early child care. (4) Modification of the "natural childbirth" technique with the addition of the rooming-in plan of maternity care, and re-emphasis on the joys of breast feeding would better prepare women for motherhood. A program for setting up maternity centers which would rely on women trained in the program and in midwifery for personnel, utilizing obstetricians for medical complications, is outlined. The centers' function would be to teach the emotional and biologic role of woman, to train for motherhood, to deliver the infants, and to act as a community center for counseling in the care of the newborn and young.

Use of interviews such as these, although providing interesting leads, cannot provide more than exterior or hasty material. Omission of questions relating to basic family structure, either that of the mother to her own family or to her marriage, gives an incomplete picture of the female role as played by these women. Women who have received instruction in natural childbirth and have become familiar with the attitudes of personnel toward childbirth and woman's function cannot be expected to give unbiased answers; they are more likely to give positive answers to related questions, and negative responses containing dissatisfaction with the program and toward motherhood. It is unfortunate that the discussion is not limited to objective findings. Instead, the data were used to plead for various convictions, but the book is written with pleasant simplicity and sincerity and the statistical analysis is admirable.

La Pneumoginecografia. By F. Marchesi, L. Oliva, V. Albano, and M. Maneschi. 134 pages with 77 illustrations. Genova, 1955, Edizioni Minerva Medica.

The diagnostic technique discussed in this monograph is not widely used in this country. It is a method of contrast radiography using air which has been introduced into the peritoneal cavity to outline the pelvic viscera. This can be done at the time of culdoscopy or by primary pneumoperitoneum. Unfortunately, the reproductions of the x-rays are poor and the reader must often take the authors' word for the interpretation of the films. However, the authors seem enthusiastic about this technique.

Grundriss und Atlas der gynakologischen Cytodiagnostik. By H. Smolka and H. J. Soost. 186 pages with 268 illustrations. Stuttgart, 1956, Georg Thieme Verlag. $28.50.

This is one of the latest books on the cytology of the female genital tract. Since the type is relatively small, there is a great deal of description in the 186 pages, including that of methods of obtaining, handling, and staining cervical smears, of normal cytology at different periods of life, of smear changes produced by various steroid hormones, infections (including Trichomonas infestation), benign cervical conditions, and by pregnancy (including abortion). The cytology of ascitic fluid, including the presence of malignant cells, is described. The relatively small section devoted to carcinomas (especially endometrial) could have been more extensive. There are a few pages describing the changes associated with radiation and these are well illustrated. In general, the illustrations are good, but there could have been more of higher magnification to give more cellular detail.

The language (German) and the price ($28.50) will limit the usefulness in this country.

The Thyroid: A Fundamental and Clinical Text. By Sidney C. Werner. 789 pages with 130 illustrations. New York, 1955, Paul B. Hoeber, Inc. $20.00.

This is truly an outstanding contribution to the literature concerning the thyroid from both the clinical and investigative viewpoints. The first 264 pages are devoted to fundamental aspects of the thyroid, including physiology, relationship of the thyrotropic secretion of the anterior pituitary, effects of steroids and stress, biochemistry of the thyroid hormone, anatomy, embryology, and laboratory methods for the evaluation of thyroid function. Of the 76 pages devoted to laboratory methods, 48 describe the use of radioiodine; this description is most complete.

The remainder of the book discusses diseases of the thyroid, thoroughly, but in a style which is conducive to easy reading and assimilation. The attitude toward therapy is very stable and intelligent in most instances.

The bibliography at the end of each section is very complete, so that one can find sufficient references for investigation of specific problems. There are 60 separate contributors, all of whom are well known in the fields they represent.

Obstetrical Anesthesia, Its Principles and Practice. By Bert S. Hershenson. 403 pages with 50 illustrations. Springfield, Ill., 1955, Charles C Thomas, Publisher. $9.50.

Designed primarily for obstetricians, this book clarifies the purposes and methods of anesthesiologists. The chapters on premedication and selection of techniques for regional and general anesthesia are good. Circulatory and respiratory derangements are discussed in another chapter. A combination of scopolamine and apomorphine is recommended as favorable for amnesia and analgesia. It is relatively safe early or late in labor. Discussion of aspiration pneumonitis would be more appropriate in the section on untoward respiratory sequelae from anesthesia. The valuable technique of single-dose pudendal block is omitted. From the general discussion in these sections, the author appears to prefer inhalation anesthesia to regional anesthesia for obstetrics.

The chapter on asphyxia neonatorum, which includes some experimental data on the physiology of intrauterine respiration, is excellent. The therapeutic value of analeptics is questioned because of their small margin of safety, and the use of carbon dioxide is properly condemned.

The technique of anesthesia for patients with medical complications, such as heart disease, diabetes, and poliomyelitis is described in another section. The bibliographic reference lists at the end of each chapter are admittedly not exhaustive. The printing is good and the index complete.

Recueil periodique de l'Encyclopédie Médico-chirurgicale. 32-33e Cahier specialisé d'obstétrique. Published under the direction of A. Laffont and E. Chome. Paris, 1956, Edition Techniques.

This special supplement discusses in detail many obstetrical problems including: intrauterine fetal embarrassment and death; diseases of the placenta and membranes with special emphasis on hydatid moles and chorionepitheliomas; clinical and radiological signs of pelvic contraction; and delivery without pain by the prophylactic use of psychotherapy.

Although this is an excellent review, no new solutions of problems are set forth.

Progress in Clinical Obstetrics and Gynecology. By T. L. T. Lewis. 594 pages with 90 illustrations. Boston, 1956, Little, Brown & Company. $12.00.

Rarely does one read a review of current progress with so much admiration and profit as I have this volume.

Mr. Lewis is a young man with exceptionally broad experience in the field of obstetrics and gynecology. He has a logical, concise mind, to which has been added a broad view of the world's literature.

There are 17 chapters dealing with obstetrics and 15 with gynecology. The first chapter in each of the two sections is devoted to changing practice. These constitute an over-all review and are followed by subjects of current interest and controversy. Obviously, the author has been limited by space in what he chooses to discuss, but he has chosen well and with discernment areas in which research is being actively carried out and advances are likely to be made.

Current available statistics of methods of treatment and results are given. These are presented in similarly arranged, clear, concise tables. Such tables are of particular value in the chapters dealing with genital carcinoma, breech presentation, and postmaturity.

The four chapters on carcinoma of the uterus deserve special mention. The widely diverse data so necessary for intelligent treatment are beautifully and logically presented. Conclusions are reached only after thorough consideration of available facts.

This book may slightly favor the English viewpoint and occasionally one suspects that the American literature has been selected because it was recent. Nevertheless, the author has accomplished well his stated purpose of presenting an account of recent development in clinical obstetrics and gynecology.

Gynecologic Cancer. By James A. Corscaden. Second edition. 546 pages with 116 illustrations. Baltimore, 1956, The Williams & Wilkins Company. $10.00.

The second edition of *Gynecologic Cancer* is a revision, moderization, and enlargement of the first. The introduction is most important, discussing incidence, probability, rate of cure, and early diagnosis. Stress is placed upon early diagnosis.

All known modalities useful in establishing the diagnosis of gynecologic cancer are discussed. The author estimates that if systematic aggressive search for gynecologic cancer were made, the survival rate might be raised to about 90 per cent.

Cervical cancer, the most common gynecologic cancer, is the most thoroughly treated tumor. The author seems to feel that radiotherapy is preferable to surgery except in isolated specific instances. The problem of injuries subsequent to treatment is dealt with.

The approach to endometrial carcinoma is logical; there will be some disagreement, however, with the conclusion that standard treatment should be the use of intracavitary radium followed in six to eight weeks by a complete abdominal hysterectomy and bilateral salpingo-oophorectomy.

It is emphasized that clinical rather than laboratory data are needed to develop a logical therapeutic program for handling neoplastic diseases of the chorion.

The problems of dealing with ovarian cancer are well covered, but this reviewer thinks that perhaps the 5 year survival rate mentioned is too high.

The discussion of the management of cancer patients and the nature of cancer is sensible and thought provoking.

La Fonction ovarienne et son exploration. By R. Vokaer. 108 pages with 54 illustrations. Paris, 1956, Masson & Cie. 850 fr.

This excellent monograph deals with the basic embryology and development of the ovary from ovum and fetus through the adult, the physiology and pathogenesis of ovulation and menstruation, the chemistry and metabolism of estrogen and progesterone, and the clinical techniques and application of the ovarian function. A discussion of history, basal temperature, endometrial changes, and alteration of vaginal mucosa is included. Dosages of estrogen and progesterone are set forth.

Tuberculosis in Obstetrics and Gynecology. By George Schaefer. 307 pages with 50 illustrations. Boston, 1956, Little, Brown & Company. $8.75.

Because the author of this book is a recognized authority on tuberculosis in obstetrics and gynecology, he brings to the discussion opinions based upon facts and not upon fancy.

The advent of chemotherapy in the treatment of tuberculosis has altered some older concepts. The entire field of chemotherapy is covered, including types of drugs, indications, contraindications, and expected results. Although chemotherapy has advanced the treatment of tuberculosis greatly, it is emphasized that it has not replaced other methods of treatment. It should be considered an adjunct to them.

There are two aspects of the book which must be criticized; these are the inclusion of excessive statistics and poor illustrations. Also, although it does not detract from the value of the book, it is a grave oversight not to have all the references included in the bibliography.

La Chirurgie pelvienne après cloisonnement abdomino-pelvien. By H. Bompart and R. Michel-Béchet. 81 pages with 15 illustrations. Paris, 1956, Masson & Cie. 750 fr.

The authors, both renowned surgeons, discuss their technique of radical pelvic surgery. Their principal objective in cancer surgery is to remove the largest possible mass of lymphatic

tissue which might be invaded. After dissection of lymph nodes, no peritonization is necessary, but the authors prefer to build up, at the beginning of the operation, a protective peritoneal barrier which will separate the abdominal cavity with its intestine from the pelvis where the septic phase of the operation is to take place. The technique and advantages of the procedure are described.

The Pregnancy Toxemias or the Encymonic Atelositeses. By G. W. Theobald. 488 pages with 50 illustrations and 27 tables. New York, 1956, Paul B. Hoeber, Inc. $15.00.

As to the title, the title page is the only place in the book where "toxemia" is spelled without the ligature "ae." Strictly amateur Greek translates the subtitle as "first-pregnancy nutritional deficiency diseases." The term is not in dictionaries and the reference given to the paper in which the author may have introduced it is erroneous, as are some other references. Authors' names are misspelled wholesale. Moreover, the page citations of the index are not always correct.

The physiology of pregnancy is reviewed: some phases, such as water metabolism, diuresis and antidiuresis, the adrenal cortex, and intraabdominal pressures are very well done. The treatment of many other aspects is superficial, out of date, and insular. Historical credits are sometimes misplaced, e.g., on page 273, "Zangemeister (1919) and Fischer (1921) were among the first to postulate that eclamptic convulsions were due to oedema of the brain." Traube and Rosenstein antedated them by at least half a century.

The main theme of the book is that the toxemias of pregnancy stem from dietary deficiencies. This opens the door for the inclusion of not only "several" eclampsias, but also hyperemesis, acute yellow atrophy of the liver, chorea gravidarum, impetigo herpetiformis, and some other human diseases as well as several diseases of other animals. Theobald writes that adequate nutrition not only would prevent these diseases, but also would decrease the incidence of puerperal infection, abortion, stillbirth, neonatal death, fetal abnormalities, twin pregnancy, placenta previa, etc.

The author sets up 16 "eclamptic criteria," which must be satisfied by any acceptable hypothesis as to causation of the disease. Against this background, he demolishes many current hypotheses but believes that his own holds up. It seems to the reviewer that one of the difficulties in the way of the dietary deficiency hypothesis is the marked association of eclampsia with primigravidity. Chronic nutritional deficiency should be aggravated by successive "parasitic" pregnancies and the incidence of eclampsia should, therefore, increase with higher parity. Theobald evades this objection by postulating mechanical factors acting in conjunction with malnutrition. These mechanical factors are specified as "the weight and bulk of the uterus, together with the upright position." He then writes, "It is evident that the mechanical factors will operate more adversely in primigravidae. . . ." It is not evident to the reviewer. Even if the mechanical factors do have less effect in multiparas, these women still have a more advanced nutritional depletion, a hair-trigger situation. Perhaps inadequate nutrition may be a predisposing factor to pre-eclampsia-eclampsia, rather than the cause.

This book is not worth the $15 asked for it.

Diagnosis and Treatment of Stress Incontinence in the Female. By J. Janssens. 156 pages with 14 illustrations. Holland, 1956, Van Gorcum and Co.

The subject of this monograph—stress incontinence—is a physical and mental burden common in parous women over 40.

Emphasis is placed upon the differential diagnosis of incontinence resulting from insufficiency of the closing mechanism of the bladder and from other defects, for irreparable damage may result from operative treatment in the presence of unrecognized disturbances.

The pathogenesis of the condition and the physiology of the mechanism of retention are obscure. Hence, attempts at treatment are empirical. Cystometrical estimations do not appear to be valuable aids, but urethrocystographs are valuable both in recognizing anatomical defects and in selecting therapy. Treatment differs with the severity of the case. Results are given of operative treatment of 335 cases (Jan. 1, 1950, to May 1, 1955). The Marshall-Marchetti vesicourethral suspension gave the most favorable overall result (88.3 per cent total remission of symptoms in 60 cases). The Aldridge sling operation was used in too few cases for evaluation of the technique. Vaginal operations appeared to be effective in mild cases; Franz levator and Martius bulbocavernosus sling repairs were superior among vaginal methods employed.

Studies on Fertility, Vol. VII of the Proceedings of the Society for the Study of Sterility. Edited by R. G. Harrison. 156 pages. Oxford, England, 1955, Blackwell Scientific Publications. $5.00.

As in previous years, the Conference of the British Society for the Study of Sterility has published in book form outstanding contributions made during the year 1955 by members of the Society. The contents include experimental and clinical research on male and female factors.

There are two articles on human male fertility, one, "Apparent Azoospermia Due to Retrograde Ejaculation; Successful Insemination With Semen Recovered From the Bladder," describes two cases of idiopathic retrograde ejaculation. Cervical insemination of the bladder ejaculate was performed successfully on two occasions for one couple. The other article, "Cytological Events in the Human Testes in Relation to Abnormalities in Sperm Morphology," correlates abnormal sperm morphology in the ejaculate with the histopathology of the testes. Many excellent illustrations are included in the discussion. These two papers are followed by five experimental studies on fertility in male animals.

In the section on female fertility, there are three clinical papers. One, "Observations on the Postcoital Test," tells of 638 postcoital tests performed in the routine investigation of 394 patients who complained of infertility. Two hundred and ten tests were made on 140 patients who apparently conceived and 428 tests on 254 patients who had not conceived. The results were analyzed in respect to quality of cervical mucus, sperm invasion and sperm activity within the mucus, as well as a combination of these factors. The second article, "Fertility in Women," deals with the fertility of women who presented themselves for donor insemination. One important conclusion was that the failure rate of 42.3 per cent reflected the incidence of female infertility not detectable by available diagnostic methods. A third paper is "Pregnancy Following Amenorrhea Resulting From Radiotherapy for Ankylosing Spondylitis." The book is concluded by four articles on the fertility of female animals.

Item

American Board of Obstetrics and Gynecology, Inc.

The next scheduled examinations (Part I), written, and review of case histories for all candidates will be held in various cities of the United States, Canada, and military centers outside the Continental United States, on Friday, Feb. 1, 1957, at 2:00 P.M.

Candidates must submit case reports to the office of the Secretary within thirty days of being notified of their eligibility to Part I.

Requests for re-examination in Part II must be received prior to Feb. 1, 1957.

Current Bulletins may be obtained by writing to:

ROBERT L. FAULKNER, M.D., SECRETARY
2105 ADELBERT ROAD
CLEVELAND 6, OHIO

ROSTER OF AMERICAN OBSTETRICAL AND GYNECOLOGICAL SOCIETIES*

(Appears in January and July)

American College of Obstetricians and Gynecologists. (1945) *President,* R. Glenn Craig. *Secretary,* John C. Ullery, Columbus, Ohio.

American Gynecological Society. (1876) *President,* Norman F. Miller. *Secretary,* Andrew A. Marchetti, Georgetown University Hospital, Washington 7, D. C. Annual meeting, The Homestead, Hot Springs, Va., May 27-29, 1957.

American Association of Obstetricians and Gynecologists. (1888) *President,* F. Bayard Carter, Durham, N. C. *Secretary,* E. Stewart Taylor, 4200 E. Ninth Ave., Denver 20, Colo. Annual meeting, The Homestead, Hot Springs, Va., Sept. 5-7, 1957.

Central Association of Obstetricians and Gynecologists. (1929) *President,* Arthur B. Hunt, Rochester, Minn. *Secretary,* Edwin J. DeCosta, 104 S. Michigan Ave., Chicago 3, Ill. Annual meeting, Hotel Fontenelle, Omaha, Neb., Oct. 17-19, 1957.

South Atlantic Association of Obstetricians and Gynecologists. (1938) *President,* John C. Burwell, Jr., Greensboro, N. C. *Secretary,* Charles H. Mauzy, Bowman Gray School of Medicine, Winston-Salem, N. C. Next meeting, Francis Marion Hotel, Charleston, S. C., Feb. 6-9, 1957.

A. M. A. Section on Obstetrics and Gynecology. *Chairman,* D. F. Kaltreider. *Secretary,* Keith P. Russell, 511 S. Bonnie Brae St., Los Angeles 57, Calif. Meetings with annual A.M.A. meetings.

Society of Obstetricians and Gynaecologists of Canada. (1944) *President,* Brian D. Best, Winnipeg, Manitoba. *Secretary,* F. P. McInnis, 280 Bloor St. W., Toronto, Ont. Annual meeting, Banff Springs Hotel, Banff, Alberta, June 21-25, 1957.

American Board of Obstetrics and Gynecology. (1930) *President,* Bayard Carter. *Secretary,* Robert L. Faulkner, 2105 Adelbert Rd., Cleveland 6, Ohio. Meeting, May 15-25, 1957.

Akron Obstetrical and Gynecological Society. (1946) *President,* Leon Moldavsky. *Secretary,* Carl J. Paternite, 159 S. Main St., Akron, Ohio. Meetings, quarterly.

Alabama Association of Obstetricians and Gynecologists. (1940) *President,* Buford Word, Birmingham, Ala. *Secretary,* Julian P. Hardy, 920 S. 19th St., Birmingham 5, Ala. Meeting, April 17, 1957, Battle House Hotel, Mobile, Ala.

Alameda County Gynecological Society. (1951) *President,* Wilson Footer. *Secretary,* Emery P. Page, 3031 Telegraph Ave., Berkeley 5, Calif. Meetings, last Wednesday of each month.

Arkansas Obstetrical and Gynecological Society. (1953) *President,* John Walter Jones. *Secretary,* Robert W. Ross, 908 Donaghey Bldg., Little Rock, Ark. Meetings, April and October.

Atlanta Obstetrical and Gynecological Society. (1954) *President,* John B. Cross. *Secretary,* William H. Grimes, 272 Boulevard, N. E., Atlanta 12, Ga. Meetings quarterly.

Birmingham Obstetrical and Gynecological Society. (1949) *President,* Paul Woodall. *Secretary,* Walter P. Batson, 1117 S. 22nd St., Birmingham 5, Ala. Meetings, September, December, February, and April.

Boston, Obstetrical Society of. (1861) *President,* Christopher J. Duncan. *Secretary,* A. Gordon Gauld, 1180 Beacon St., Brookline 46, Mass. Meetings, January, February, March, April, October, and November.

Bronx Gynecological and Obstetrical Society. (1924) *President,* Sol S. Schiffrin. *Secretary,* Bernard Lapan, 1882 Grand Concourse, Bronx 57, N. Y. Meetings, fourth Monday, October through April, inclusive.

Brooklyn Gynecological Society. (1890) *President,* Henry Mehldau. *Secretary,* Warren A. Lapp, 731 E. 22nd St., Brooklyn 10, N. Y. Meetings, third Wednesday, October, November, January, February, March, April, and May.

Buffalo Obstetrical and Gynecological Society. (1946) *President,* Robert E. O'Connor. *Secretary,* Chester Kaminski, 333 Linwood Ave., Buffalo 9, N. Y. Meetings, first Tuesday, October through May.

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*Changes, omissions, and corrections must be received by the publisher two months in advance, by May 1 for the July Roster and by November 1 for the January Roster. Please address The C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, Mo. The number after the Society's name is the year of founding. For further information, address the respective secretaries.

Central New York Association of Gynecologists and Obstetricians. (1938) *President,* Keith B. Preston. *Secretary,* William V. Redfield, 1502 State Tower Bldg., Syracuse 2, N. Y. Meetings, second Tuesday, January, March, May, September, and November.

Chicago Gynecological Society. (1878) *President,* Ronald R. Greene. *Secretary,* Clyde J. Geiger, 4753 Broadway, Chicago 40, Ill. Meetings, third Friday, October through June.

Cincinnati Obstetrical and Gynecological Society. (1876) *President,* John G. Fleming. *Secretary,* Edward Alberts, 199 Wm. Howard Taft Rd., Cincinnati 19, Ohio. Meetings, third Thursday, September through June.

Cleveland Society of Obstetrics and Gynecology. (1947) *President,* Ralph Dial. *Secretary,* Richard Glove, 20119 Van Aken Blvd., Shaker Heights 22, Ohio. Meetings, fourth Monday, September, November, January, March, and May.

Columbus Obstetric-Gynecologic Society. (1944) *President,* James B. Patterson. *Secretary,* Harry E. Ezell, Jr., 81 S. Fifth St., Columbus, Ohio. Meetings, last Wednesday of month, September through May, except December.

Connecticut Society of American Board Obstetricians and Gynecologists, Inc. (1952) *President,* Lewis P. James. *Secretary,* Joseph Klein, 435 Farmington Ave., Hartford 5, Conn. Meetings twice a year.

Dallas-Fort Worth Obstetric and Gynecologic Society. (1948) *President,* D. J. Harrell. *Secretary,* H. I. Kantor, 3534 Maple Ave., Dallas 19, Texas. Meetings, last Thursday, March and October.

Dayton Obstetrical and Gynecological Society. (1937) *President,* E. E. Pinnell. *Secretary,* J. C. Burt, 1130 Fidelity Bldg., Dayton, Ohio. Meetings, third Wednesday, September through May.

Denver Gynecological and Obstetrical Society. (1942) *President,* N. Paul Isbell. *Secretary,* Charles R. Freed, 1809 E. 18th Ave., Denver 18, Colo. Meetings, first Monday of every month, October through May, inclusive, unless otherwise notified.

El Paso County Obstetrical and Gynecological Society. (1948) *President,* Erich Spier. *Secretary,* Alvin L. Perry, 209 Medical Arts Bldg., El Paso, Texas. Meetings, last Thursday of month.

Florida Obstetric and Gynecologic Society. (1948) *President,* Carnes Harvard. *Secretary,* Bert Fletcher, Tallahassee, Fla. Meeting, May, 1957.

Georgia State Obstetrical and Gynecological Society. (1951) *President,* Hartwell Boyd. *Secretary,* J. Lon King, Jr., 817 Persons Bldg., Macon, Ga. Meetings, spring and fall.

Harris, John Warton, Obstetrical Society. (1953) *President,* E. Russell Muntz. *Secretary,* Alice D. Watts, 324 E. Wisconsin Ave., Milwaukee 2, Wis.

Honolulu Obstetrical and Gynecological Society. (1947) *President,* Rodney T. West. *Secretary,* Fugate Carty, Straub Clinic, Thomas Square, Honolulu, Hawaii. Meetings, third Monday of each month at the Mabel Smythe Memorial Bldg.

Houston Gynecological and Obstetrical Society. *President,* Herman L. Gardner. *Secretary,* Melville L. Cody, 4115 Fannin St., Houston, Texas. Meetings, January, March, May, and October, 1957.

Indianapolis Obstetrical and Gynecological Society. (1947) *President,* Lawson J. Clark. *Secretary,* John F. Spahr, Jr., 3440 N. Meridian St., Indianapolis 8, Ind. Meetings, second Wednesday in January, April, and October.

Interurban Obstetrical and Gynecological Society. (1949) *President,* Clyde L. Randall, Buffalo, N. Y. *Secretary,* E. R. Duggan, 16 N. Goodman St., Rochester 7, N. Y. Meeting, October, 1957.

Iowa Obstetrical and Gynecological Society. *President,* Robert M. Collins, Council Bluffs, Iowa. *Secretary,* W. B. Goddard, University Hospitals, Iowa City, Iowa. Meetings, May and November.

Kansas City Gynecological Society. (1922) *President,* James E. Keeler. *Secretary,* Floyd C. Atwell, 4620 J. C. Nichols Parkway, Kansas City, Mo. Meetings, September, November, January, March, and May.

Kentucky Obstetrical and Gynecological Society. (1947) *President,* Robert Orr, Mayfield, Ky. *Secretary,* Ed. Masters, 107 Fairmeade Rd., Louisville, Ky. Annual meeting, spring, 1957.

Long Beach Obstetrical and Gynecological Society. (1954) *President,* Geneva Beatty. *Secretary,* Sydney G. Willner, 911 East San Antonio Drive, Long Beach 7, Calif. Meetings, first Tuesday of March, June, September, and December.

Los Angeles Obstetrical and Gynecological Society. (1914) *President,* Ralph Walker. *Secretary,* Alphonsus M. McCarthy, 3757 Wilshire Blvd., Los Angeles, Calif. Meetings, second Tuesday, September, November, January, and March.

Louisville Obstetrical and Gynecological Society. *President,* Hugh P. Adkins. *Secretary,* Douglas M. Haynes, 323 E. Chestnut St., Louisville 2, Ky. Meetings, fourth Monday, September, October, November, January, February, March, April, and May.

Madison Obstetrical and Gynecological Society. (1950) *President* and *Secretary,* William C. Mussey, 113 N. Carroll St., Madison, Wis. Meetings, first Tuesday each month, September through June.

Maryland, Obstetrical and Gynecological Society of. (1929) *President,* Royce Hodges. *Secretary,* Harry M. Beck, 700 N. Charles St., Baltimore 1, Md. Meetings, second Thursday, October, December, February, and May.

Memphis Obstetrical and Gynecological Society. (1950) *President,* Carey Bringle. *Secretary,* Robert M. Ruch, 899 Madison Ave., Memphis, Tenn. Meetings, second Tuesday, October, November, January, March, and May.

Miami Obstetrical and Gynecological Society. (1946) *President,* Reuben B. Chrisman, Jr. *Secretary,* George R. Gage, 365 Alcazar Ave., Coral Gables 34, Fla. Meetings, second Thursday, January, March, May, and November.

Michigan Society of Obstetricians and Gynecologists. (1924) *President,* Carl F. Shelton. *Secretary,* E. Bruce Foster, 853 Fisher Bldg., Detroit 2, Mich. Meetings, first Tuesday, October through May.

Milwaukee Gynecological Society. (1951) *President,* Lionel T. Servis. *Secretary,* Carlton W. Wirthwein, 425 East Wisconsin Ave., Milwaukee 2, Wis. Meetings, last Monday, January, March, May, and November.

Minneapolis Obstetrical and Gynecological Society. (1955) *President,* John A. Haugen. *Secretary,* Francis M. Swain.

Minnesota Obstetrical and Gynecological Society. *President,* Frederick L. Schade. *Secretary,* Edward A. Banner, 200 First St., S.W., Rochester, Minn. Meetings, spring and fall. Next meeting, Duluth, Minn., April 27, 1957.

Mississippi Obstetrical and Gynecological Society. (1947) *President,* Ross F. Bass, Jackson, Miss. *Secretary,* Blanche Lockard, 625 Fondren Pl., Jackson, Miss. Meetings, May and November.

Mobile County Obstetrical and Gynecological Society. (1949) *President,* H. B. Dowling. *Secretary,* J. R. Mighell, 1302 Government St., Mobile, Ala. Meetings, quarterly when called.

Montgomery County (Ohio) Obstetrical and Gynecological Society. (1937) *President,* L. O. Fredericks. *Secretary,* A. A. Kunnen, 406 Harries Bldg., Dayton, Ohio. Meetings, third Wednesday of each month.

Montana Obstetrical and Gynecological Society. (1946) *President,* Leonard W. Brewer, Missoula, Mont. *Secretary,* Robert H. Leeds, Chinook, Mont. Annual meeting, Butte, Mont., April, 1957.

Nashville Obstetrical and Gynecological Society. (1955) *President,* Joe Anderson. *Secretary,* H. M. Pace, Jr., 610 Gallatin Rd., Nashville, Tenn. Four meetings per year from October to May.

Nassau Obstetrical Society. (1944) *President,* David G. Warden. *Secretary,* A. F. Rowsom, 21 Weir Lane, Locust Valley, N. Y. Meetings, second Monday, October, December, February, and April.

New England Obstetrical and Gynecological Society. (1929) *President,* Roland McSweeney. *Secretary,* William A. Lynch, 1101 Beacon St., Brookline 46, Mass. Meetings, spring and fall.

New Haven Obstetrical and Gynecological Society. (1946) *President,* Stanley Hitchins. *Secretary,* Virginia M. Stuermer, 42 Trumbull St., New Haven 10, Conn. Meetings, October, November, January, March, and May.

New Jersey Obstetrical and Gynecological Society. (1947) *President,* Sam. Gordon Berkow. *Secretary,* Paul Grossbard, 162 Lexington Ave., Passaic, N. J. Meetings, October and April.

New Mexico Obstetrical and Gynecological Society. (1947) *President,* James W. Wiggins. *Secretary,* Robert P. George, 4800 Gibson Blvd., S. E., Albuquerque, N. Mex. Meetings, quarterly, January, May, August, and October.

New Orleans Gynecological and Obstetrical Society. (1924) *President,* Isadore Dyer. *Secretary,* C. Gordon Johnson, 3636 St. Charles Ave., New Orleans 15, La. Meetings, October, November, January, March, and May.

New York Obstetrical Society. (1863) *President,* Edward H. Dennen. *Secretary,* George L. Bowen, 101 East 74th St., New York 21, N. Y. Meetings, second Tuesday, October through May.

North Carolina Obstetrical and Gynecological Society. (1932) *President,* R. A. Ross. *Secretary,* James A. Crowell, 412 N. Church St., Charlotte, N. C. Meeting, Midpines Club, Southern Pines, N. C., May 4 and 5, 1957.

North Dakota Society of Obstetrics and Gynecology. (1938) *President,* C. B. Darner. *Secretary,* John Gillam, 807 Broadway, Fargo, N. D. Meetings, May and September, 1957.

Northeastern New York Obstetrical and Gynecological Society. (1935) *President,* Arthur R. Wilsey. *Secretary,* James L. Lanzillo, 1938 Fifth Avenue, Troy, N. Y. Meetings, third Thursday, January, May, and October.

Oklahoma City Obstetrical and Gynecological Society. (1940) *President,* Robert D. Anspaugh. *Secretary,* Sterling T. Crawford, Osler Bldg., Oklahoma City, Okla. Meetings, third Wednesday of February, April, June, October, and December.

Omaha Obstetrical and Gynecological Society. (1947) *President,* Leon S. McGoogan. *Secretary,* W. H. Taylor, Jr., 3807 Cuming, Omaha, Neb. Meetings, third Wednesday, March, April, May, September, October, and November.

Oregon Society of Obstetricians and Gynecologists. *President,* Gordon McGowan. *Secretary,* David W. James, 4212 N. E. Broadway, Portland 13, Ore. Meetings, third Friday, October through May, except December.

Pacific Coast Obstetrical and Gynecological Society. (1931) *President,* Bernard J. Hanley, Los Angeles, Calif. *Secretary,* Donald W. DeCarle, 2000 Van Ness Ave., San Francisco, Calif. Next meeting, Oct. 31–Nov. 2, 1957.

Pacific Northwest Obstetrical and Gynecological Association. (1947) *President,* J. E. Harrison. *Secretary,* Earl L. Hall, 1220 Central Ave., Great Falls, Mont.

Philadelphia, Obstetrical Society of. (1868) *President,* George A. Hahn. *Secretary,* Paul A. Bowers, 2031 Locust St., Philadelphia 3, Pa. Meetings, first Thursday, October through May.

Pittsburgh Obstetrical and Gynecological Society. (1934) *President,* E. F. Williams. *Secretary,* Michael A. Guthrie, 128 Carlton House, 550 Grant St., Pittsburgh 19, Pa. Meetings, first Monday, October through May, except January.

Portland Society of Obstetricians and Gynecologists. (1928) *President,* Ivan I. Langley. *Secretary,* James M. Whitely, 207 Medical Arts Bldg., Portland, Ore. Meetings, fourth Wednesday, September through May.

Queens Gynecological Society. (1948) *President,* J. Gibson Hill. *Secretary,* David Connors, 166-05 Highland Ave., Jamaica 32, N. Y. Meetings, second Wednesday, October, December, February, and April.

Rochester Academy of Medicine, Obstetrics and Gynecology Section. (1939) *President,* Donald Kariher. *Secretary,* Robert A. Clark, 16 N. Goodman St., Rochester, N. Y. Meetings, spring, fall, and winter.

St. Louis Gynecological Society. (1924) *President,* William H. Vogt, Jr. *Secretary,* Eugene G. Hamilton, 8505 Delmar Blvd., St. Louis 24. Meetings, second Thursday, October, December, February, and April.

San Antonio Obstetrical and Gynecological Society. *President,* G. G. Passmore. *Secretary,* Frank M. Posey, Jr., 641 Moore Bldg., San Antonio, Texas. Meetings, first Monday of the month.

San Diego Gynecological Society. (1937) *President,* George H. Derieux. *Secretary,* Wilton Lewis, 525 Hawthorn, San Diego 1, Calif. Meetings, as announced.

San Francisco Gynecological Society. (1929) *President,* Charles T. Hayden. *Secretary,* Edmund F. Anderson, 2445 Ocean Ave., San Francisco 27, Calif. Meetings, second Friday, October through April.

Seattle Gynecological Society. (1941) *President,* John Clancy. *Secretary,* Paul Peterson, 1664 Medical-Dental Bldg., Seattle, Wash. Meetings, third Wednesday, January, March, April, May, September, October, and November.

South Carolina Obstetrical and Gynecological Society. (1946) *President,* Herbert Blake. *Secretary,* James E. Bell, Jr., 325 W. Calhoun St., Sumter, S. C. Meeting, spring.

Southwest Obstetrical and Gynecological Society. (1951) *President,* Jesse Rust, San Diego, Calif. *Secretary,* Zeph B. Campbell, 550 W. Thomas Rd., Phoenix, Ariz.

Texas Association of Obstetricians and Gynecologists. (1930) *President,* Carey Hiett, Fort Worth, Texas. *Secretary,* Oran V. Prejean, 4317 Oak Lawn Ave., Dallas 19, Texas. Annual meeting, Gunter Hotel, San Antonio, Texas, Feb. 23, 1957.

Tulsa Obstetrical and Gynecological Society. (1955) *President,* Walter B. Sanger. *Secretary,* J. E. Goldberg, 212 Utica Square Medical Center, Tulsa, Okla. Five meetings per year.

Utah Obstetrical and Gynecological Society. (1948) *President,* Morgan S. Coombs. *Secretary,* Von G. Holbrook, 508 East South Temple, Salt Lake City 2. Meetings, second Tuesday of October, December, March, and May, or as announced.

Virginia Obstetrical and Gynecological Society. (1936) *President,* Millard B. Savage. *Secretary,* Brock D. Jones, Jr., 1204 Colonial Ave., Norfolk, Va. Meetings, April and October.

Washington Gynecological Society. (1933) *President,* J. Keith Cromer. *Secretary,* Robert B. Nelson, Jr., 1824 Massachusetts Ave., N. W., Washington 6, D. C. Meetings, October, December, January, March, and May.

Washington State Obstetrical Association. (1936) *President,* Robert M. Campbell. *Secretary,* Glen G. Rice, 1420 Seneca, Seattle 1, Wash. Meetings, April and October.

West Texas Obstetrical and Gynecological Society. (1954) *President,* O. R. Hand, Lubbock, Texas. *Secretary,* D. D. Wall, 234 W. Beauregard Ave., San Angelo, Texas.

Wisconsin Society of Obstetrics and Gynecology. (1940) *President,* Alice Watts. *Secretary,* William V. Luetke, 1023 Regent St., Madison 5, Wis. Meetings, spring and fall.



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1. Shook, D. M.: Am. Pract. & Digest Treat. 7:917 (June) 1956.
2. Schneeberg, N. G.; Perczek, L.; Nodine, J. H., and Perloff, W. H.: J.A.M.A. *161*:1062 (July 14) 1956.

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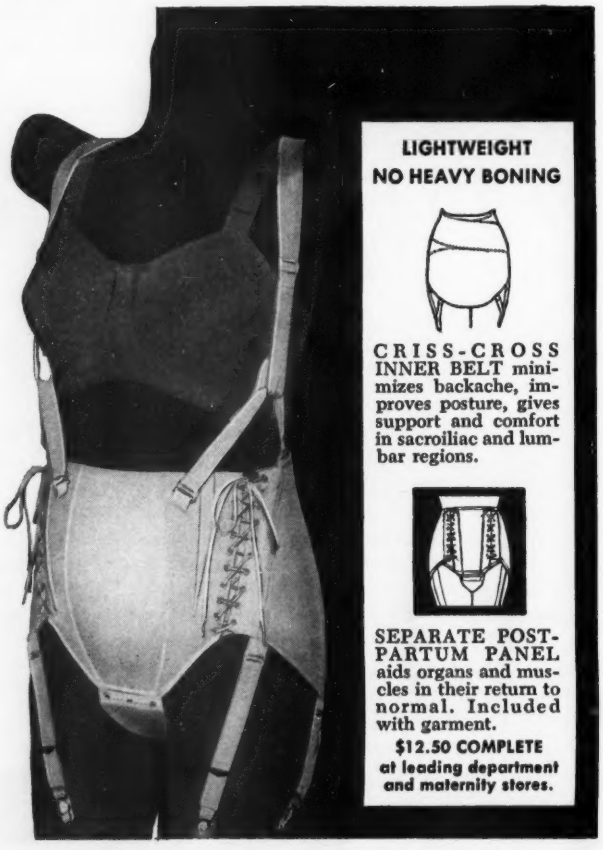
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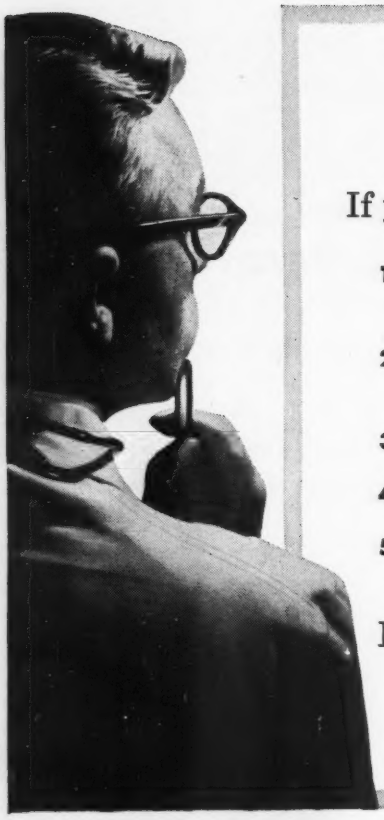
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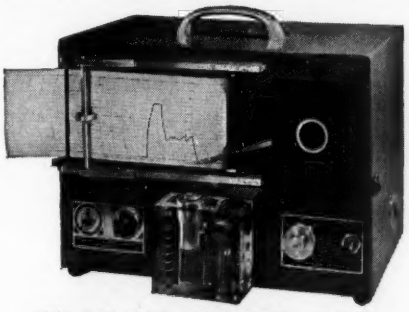
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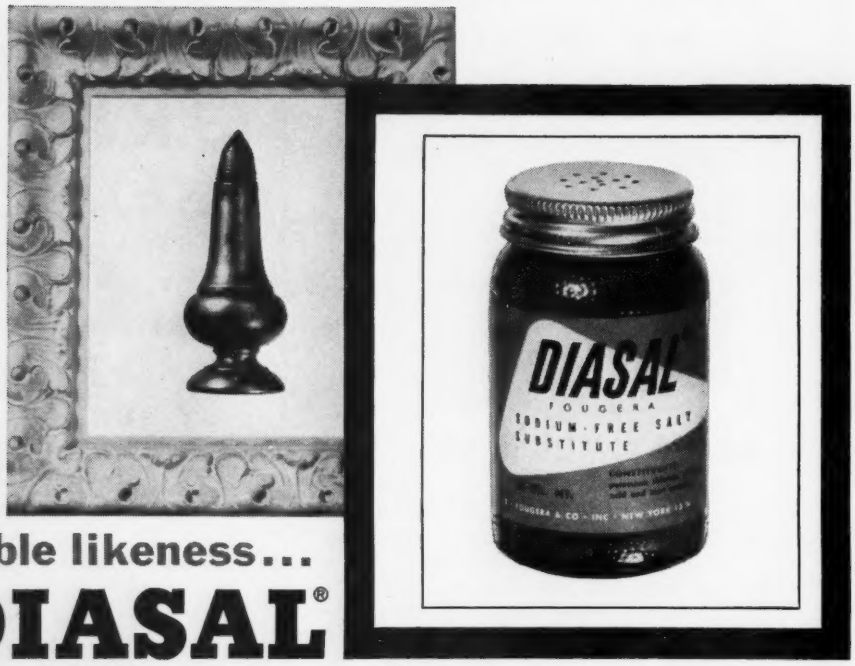
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